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(54) Title: NOVEL SUPPOSITORY FORM COMPRISING AN ACID-LABILE ACTIVE COMPOUND (57) Abstract <p>A new administration form for acid-labile active compounds is described. The administration form is a suppository, in particular for rectal administration.</p>		

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Novel suppository form comprising an acid-labile active compound**Technical field**

The present invention relates to the field of pharmaceutical technology and describes a novel administration form comprising an acid-labile active compound, in particular an acid-labile proton pump inhibitor. The novel administration form is a suppository, in particular for rectal administration. Furthermore, the invention also relates to a process for the production of the administration form and preparations which can be used for the production of the administration form.

Prior art

Acid-labile proton pump inhibitors (H^+/K^+ ATPase inhibitors), in particular pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, such as are disclosed, for example, in EP-A-0 005 129, EP-A-0 166 287, EP-A-0 174 726 and EP-A-0 268 956, are of great importance on account of their H^+/K^+ ATPase-inhibiting action in the therapy of diseases which result from increased gastric acid secretion. Examples of already commercially available active compounds from this group are 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: omeprazole), 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: pantoprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: lansoprazole) and 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]methylsulfinyl]-1H-benzimidazole (INN: rabeprazole).

Because of their strong tendency to decompose in a neutral and, in particular, acidic environment, strongly colored decomposition products being formed, it is necessary to protect the active compounds in pharmaceutical administration forms from the action of acids and moisture and destruction by undesired interaction with pharmaceutical auxiliaries. For example, the strongly acid-labile pyridin-2-ylmethylsulfinyl-1H-benzimidazoles for oral administration forms are processed in the tablet core or in pellets in the form of their alkaline salts, for example as sodium salts, or together with alkaline substances.

The preparation of administration forms for acid-labile proton pump inhibitors for oral administration is described, for example, in EP-A-0 244 380, EP-A-0 519 365, EP-A-0 342 522, EP-A-0 277 741, WO 96/01623, WO 96/01624, WO 96/01625 and WO 97/25030.

In certain groups of patients, the oral administration of an active compound is not possible or is made difficult, for example in the case of patients having a hypersensitivity to taste impulses, in the case of difficulty in swallowing, after stomach operations or in patients in intensive care units. In these cases, the administration of an active compound can be effected by means of a suppository.

EP-0 645 140 describes compositions for rectal administration in which pyridin-2-ylmethylsulfinyl-1H-benzimidazoles and salts of fatty acids having 6-20 C atoms are present mixed in a base for rectal administration.

In WO 97/34580, a suppository for acid-labile active compounds is described which, in addition to the active compound, contains poloxamer and hydrophilic natural polymers as auxiliaries.

EP-0 444 625 discloses omeprazole compositions for rectal administration, which contain omeprazole as an active compound, a mixture of polyethylene glycols or a mixture of hard fat and sodium lauryl sulfate as well as a soluble basic amino acid.

Description of the invention

It is an object of the present invention to provide a novel, stable suppository form for acid-labile active compounds.

It has now surprisingly been found that this object can be achieved by a suppository which comprises a plurality of individual active compound units, the acid-labile active compound in the individual active compound units being surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.

The subject of the invention is a suppository for acid-labile active compounds, comprising at least one pharmaceutical auxiliary and a plurality of individual active compound units, wherein the acid-labile active compound in the individual active compound units is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.

A preferred subject of the invention is a suppository for acid-labile active compounds, comprising at least one pharmaceutical auxiliary and a plurality of individual active compound units, wherein the acid-labile active compound in the individual active compound units is surrounded by a mixture of at least one sterol and at least one polymer.

Further subjects follow from the patent claims.

The plurality of individual active compound units in the sense of the invention is a plurality of individual units (multiple individual units) in which at least one active compound particle is present surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.

Further subject of the invention is an active compound unit comprising an acid-labile active compound, wherein the acid-labile active compound is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.

The particle size of the individual units is advantageously less than 200 μm , in particular less than 100 μm . Preferably, the particle size is in the range from 2 μm to 50 μm , particularly preferably in the range from 4 μm to 20 μm .

Acid-labile active compounds in the sense of the present invention are, in particular, acid-labile proton pump inhibitors.

Acid-labile proton pump inhibitors (H^+/K^+ ATPase inhibitors) which may be mentioned in the sense of the present invention are, in particular, substituted pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, such as are disclosed, for example, in EP-A-0 005 129, EP-A-0 166 287, EP-A-0 174 726, EP-A-0 184 322, EP-A-0 261 478 and EP-A-0 268 956. Preferably, mention may be made here of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: omeprazole), 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: pantoprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: lansoprazole) and 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl)methylsulfinyl]-1H-benzimidazole (INN: rabeprazole).

Further acid-labile proton pump inhibitors, for example substituted phenylmethylsulfinyl-1H-benzimidazoles, cycloheptapyridin-9-ylsulfinyl-1H-benzimidazoles or pyridin-2-ylmethylsulfinylthienimidazoles are disclosed in DE-A-35 31 487, EP-A-0 434 999 or EP-A-0 234 485. Mention may be made by way of example of 2-[2-(N-isobutyl-N-methylamino)benzylsulfinyl]benzimidazole (INN: leminoprazole) and 2-(4-methoxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ylsulfinyl)-1H-benzimidazole (INN: nepaprazole).

The acid-labile proton pump inhibitors are chiral compounds. The term acid-labile proton pump inhibitor also includes the pure enantiomers of the acid-labile proton pump inhibitors and their mixtures in any mixing ratio including the racemates. Enantiomerically pure acid-labile proton pump inhibitors are disclosed, for example, in WO 92/08716. Esomeprazole may be mentioned by way of example.

The acid-labile proton pump inhibitors are present here as such or preferably in the form of their salts with bases. Examples of salts with bases which may be mentioned are sodium, potassium, magnesium or calcium salts. If desired, the salts of the acid-labile proton pump inhibitors with bases can also be present in hydrate form. Such a hydrate of the salt of an acid-labile proton pump inhibitor with a base is disclosed, for example, in WO 91/19710.

Particularly preferred acid-labile proton pump inhibitors which may be mentioned are pantoprazole sodium and pantoprazole sodium sesquihydrate (= pantoprazole sodium \times 1.5 H₂O).

The sterol is preferably a phytosterol or a zoosterol. Phytosterols which may be mentioned by way of example are ergosterol, stigmasterol, sitosterol, brassicasterol and campesterol. Zoosterols which may be mentioned by way of example are cholesterol and lanosterol. If desired, mixtures of sterols can also be present.

The polymer is preferably a polymer having nonacidic groups. Polymers which may be mentioned by way of example are polyvidone (e.g. Kollidon 17, 30 and 90 from BASF), vinylpyrrolidone/vinyl acetate copolymer and polyvinyl acetate. Cellulose ethers such as, for example, methylcellulose, ethylcellulose (Ethocel) and hydroxypropylmethylcellulose and cellulose esters (e.g. cellulose acetate phthalate) may furthermore be mentioned. If desired, mixtures of polymers can also be present.

The fatty alcohol is preferably a linear, saturated or unsaturated primary alcohol having 10-30 carbon atoms. Fatty alcohols which may be mentioned by way of example are cetyl alcohol, myristyl alcohol or stearyl alcohol. If desired, mixtures of fatty alcohols can also be present.

The amount (in % by weight) of active compound in the individual active compound unit is advantageously 1-90%. In case of units in which at least one active compound particle is present, surrounded by a mixture of at least one sterol and at least one polymer the amounts of sterol and of polymer are in each case advantageously 5-80%. Preferably, the amount of active compound is 10-50%, the amount of sterol is 10-40% and the amount of polymer is 10-50%.

In case of units in which at least one active compound particle is present, surrounded by at least one fatty alcohol, preferably the amount of active compound is 2-70 % and the amount of fatty alcohol is 30-98 %.

In case of units in which at least one active compound particle is present, surrounded by at least one fatty alcohol and at least one sterol, preferably the amount of active compound is 2-70 %, the amount of fatty alcohol is 20-90 % and the amount of sterol is 8-50 %.

In case of units in which at least one active compound particle is present, surrounded by at least one fatty alcohol and at least one polymer, preferably the amount of active compound is 10-60 %, the amount of fatty alcohol is 10-50 % and the amount of polymer is 10-40 %.

In case of units in which at least one active compound particle is present, surrounded by at least one fatty alcohol, at least one polymer and at least one sterol, preferably the amount of active ingredient is 2-70 %, the amount of fatty alcohol is 20-85 %, the amount of polymer is 2-25 % and the amount of sterol is 10-50 %.

It is possible for the person skilled in the art, on account of his/her expert knowledge, to select the best suited sterols, polymers and fatty alcohols depending on the active compound.

The individual active compound units can be prepared, for example, by spray-congealing (spray-solidification) or preferably by spray-drying. Preferably spray-drying is used for the preparation of individual active compound units in which the active compound is surrounded by a mixture of at least one sterol and at least one polymer. Spray-drying takes place from a suitable solvent. Suitable solvents for the spray-drying are preferably those in which the sterol and the polymer are soluble, while the active compound is insoluble. Suitable solvents can also be solvent mixtures.

If an acid-labile proton pump inhibitor, in particular a substituted pyridin-2-ylmethylsulfinyl-1H-benzimidazole, is employed as the active compound, the suitable solvents are, for example, hydrocarbons, chlorinated hydrocarbons and ethyl acetate. Hydrocarbons which may be mentioned are, in particular, linear or branched alkanes or alternatively cycloalkanes. Examples of linear alkanes are pentane, hexane and heptane. Examples of branched alkanes which may be mentioned are 2-methylpentane and 3-methylpentane. Examples of cycloalkanes which may be mentioned are cyclohexane and cyclopentane. If desired, mixtures of the hydrocarbons such as, for example, petroleum ether can also be employed. As a chlorinated hydrocarbon, chloroform and preferably dichloromethane may be mentioned.

On account of his/her expert knowledge in the field of spray-drying and, if necessary, by means of customary tests, it is possible for the person skilled in the art, depending on the active compound employed, to select the best suited sterols, polymers and solvents.

For spray-drying, the sterol and the polymer are dissolved in the suitable solvent and the active compound is suspended therein. If desired, the active compound can also be suspended first and the sterol and polymer then dissolved. The suspension obtained is then sprayed in a spray-dryer.

Spray-drying is carried out in a manner known per se. A detailed presentation of this technique is found in K. Masters, *Spray Drying Handbook*, 5th edition 1991, and J. Broadhead, S. K. Edmond Ronan, C. T. Rhodes, *The Spray Drying of Pharmaceuticals*, *Drug Dev. Ind. Pharm.* 18, 1169 (1992). The principle of spray-drying consists in breaking down a solution or suspension of the product to be dried into fine droplets and drying it using a hot stream of gas. The solid component remaining after evaporation of the solvent is separated off from the stream of gas by means of a cyclone and/or by a filter unit and collected.

Possible drying gases are, in particular, air and preferably nitrogen. The gas inlet temperature depends on the solvent.

Further subject of the invention is a preparation comprising an acid-labile active compound, at least one sterol and at least one polymer obtainable by spray-drying of a suspension of the acid-labile active compound in a solution of the sterol and the polymer in a suitable solvent.

Preferably spray-congealing is used for the preparation of individual active compound units in which the active compound is surrounded by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.

For spray-congealing the fatty alcohol is fused and, if desired, the polymer and/or the sterol are dissolved therein to give a homogeneous solution. The active compound is then suspended in the solution. The suspension obtained is then sprayed in a spray-dryer.

Spray-congealing is carried out in a manner known per se. A detailed presentation of this technique is found for example in P.B. Deasy, *Microencapsulation and Related Drug Process* (1984).

Further subject of the invention is a preparation comprising an acid-labile active compound, at least one fatty alcohol or a mixture of at least one fatty alcohol and at least one polymer and/or sterol obtainable by spray-congealing of a suspension of the acid-labile compound in a solution, if desired, of the polymer and/or sterol in the fatty alcohol.

The particle size of the active compound used in the spray-drying or spray-congealing process is advantageously less than 100 μm preferably less than 40 μm . Preferably, the particle size is in the range from 1-20 μm , particularly preferably in the range from 3-15 μm . Such particle size of the active compound for example can be achieved by milling the active compound in a suitable mill.

The individual active compound units, subsequently also designated as preparations, can then serve as a base for the production of the suppositories according to the invention.

Preferred suppositories which may be mentioned in this case are those which are suitable for rectal administration. The suppositories according to the invention are in this case prepared in a manner known to the person skilled in the art. For example, a suitable suppository base is fused and a preparation according to the invention is suspended therein. The suspension obtained is then brought into a form customary for suppositories. In particular, the suspension is cast to give a suppository shape suitable for rectal administration. Suitable suppository bases which may be mentioned are, for example, the hard fats customarily used for the production of rectal suppositories (subsequently also designated as *Adeps solidus* or *Adeps neutralis*). Hard fats are mixtures of mono-, di- and triglycerides which are obtained by esterification of fatty acids (European Pharmacopeia, 3rd edition 1997, Deutscher Apotheker Verlag Stuttgart, p. 1022; The United States Pharmacopeia, USP23, NF18). Such hard fats are commercially available, for example, under the name Witepsol® (e.g. Witepsol® H12 or Witepsol® W31). If desired, further pharmaceutically acceptable auxiliaries, such as, for example, stabilizers,

consistency-improving additives or auxiliaries which bring about a uniform distribution of the active compound in the suppository base, can be added.

The suppositories according to the invention contain the acid-labile active compound in a dose customary for the treatment of the appropriate disorder. The suppositories according to the invention comprising acid-labile proton pump inhibitors are suitable for the treatment and prevention of all diseases for the treatment or prevention of which pyridin-2ylmethylsulfinyl-1H-benzimidazoles are employed. In particular the suppositories according to the invention can be employed in the treatment of diseases of the stomach. Thus, the suppositories according to the invention contain between 1 and 500 mg, preferably between 5 and 60 mg, of an acid-labile proton pump inhibitor. Examples which may be mentioned are suppositories which contain 10, 20, 40 or 50 mg of pantoprazole sodium sesquihydrate. The daily dose (e.g. 40 mg of active compound) can in this case be administered in the form of a single administration or in several administrations using the suppositories according to the invention.

The suppositories comprising acid labile compounds according to the invention can also be combined with other active compounds, either in fixed or in free combination. Fixed combination in this connection relates to an administration form wherein all active compounds are present in a single dosage unit. Free combination in this connection relates to an administration form, wherein the active compounds are present in separated dosage units. In connection with suppositories comprising acid-labile proton pump inhibitors a combination with antimicrobially active compounds or NSAIDs (non steroidal anti inflammatory drugs) may be mentioned. Particularly mention may be made of a combination with antimicrobially active compounds which can be used in the control of *Helicobacter pylori* (*H. pylori*).

Examples of suitable antimicrobially-active ingredients (active against *Helicobacter pylori*) are enumerated in European Patent Application EP-A-282131. These active ingredients include, for example, bismuth salts (such as bismuth subcitrate or bismuth subsalicylate), sulfonamides, nitrofurans (such as nitrofurazone, nitrofurantoin or furazolidone), metronidazole, tinidazole, nimorazole or antibiotics. Examples of antibiotics which may be mentioned in this connection are, arranged according to particular classes of active ingredient: aminoglycosides, such as gentamicin, neomycin, kanamycin, amikacin or streptomycin; macrolides, such as erythromycin, azithromycin, clarithromycin, clindamycin or rifampicin; penicillins, such as penicillin G, penicillin V, ampicillin, mezlocillin or amoxicillin; polypeptides, such as bacitracin or polymyxin; tetracyclines, such as tetracycline, chlorotetracycline, oxytetracycline, minocycline or doxycycline; carbapenems, such as imipenem, loracarbef, meropenem or panipenem; cephalosporins, such as cefalexin, cefoxitin, cefuroxime axetil, cefotaxime, cefpodoxime proxetil, cefaclor, cefadroxil or cephalothin; gyrase inhibitors, such as ciprofloxacin, norfloxacin, ofloxacin or pefloxacin; or other different antibiotics, such as chloramphenicol. Particularly worthy of mention in this connection is also the combination of a plurality of antimicrobially-active ingredients, for example the combination of a bismuth salt and/or tetracycline with metronidazole, or the combination of amoxicillin or clarithromycin with metronidazole and amoxicillin with clarithromycin.

Particularly worthy of mention in this connection is also administration of a proton pump inhibitor together with a plurality of antimicrobially-active ingredients, for example with the combination of a bis-muth salt and/or tetracycline with metronidazole or with the combination of amoxicillin or clarithromycin or with metronidazole.

The preparation of suppositories according to the invention is described by way of example below. The examples below illustrate the invention in greater detail without restricting it.

Production of the preparations by spray-drying**Example 1**

7.0 g of cholesterol and 5.0 g of Ethocel are dissolved in 100 ml of dichloromethane. 5.0 g of pantoprazole sodium sesquihydrate are suspended in the solution. The suspension is spray-dried in a laboratory spray-dryer (Büchi Mini Spray Dryer B191). Spray conditions: drying gas nitrogen, inlet temperature 51°C; pump output 10%. A white, free-flowing powder is obtained.

Example 2

5.0 g of cholesterol and 5.0 g of Kollidon 17 are dissolved in 80 ml of dichloromethane. 5.0 g of omeprazole magnesium are suspended in the solution. The suspension is spray-dried in a laboratory spray-dryer (Büchi Mini Spray Dryer B191). Spray conditions: drying gas nitrogen, inlet temperature 51°C; pump output 10%. A white, free-flowing powder is obtained.

Example 3

5.0 g of cholesterol and 8.0 g of polyvidone 17 PF are dissolved in 60 ml of dichloromethane. 5.0 g of pantoprazole sodium sesquihydrate are suspended in the solution. The suspension is spray-dried in a laboratory spray-dryer (Büchi Mini Spray Dryer B191). Spray conditions: drying gas nitrogen, inlet temperature 52°C; pump output 12%. A white, free-flowing powder is obtained.

Example 4

5.0 g of cholesterol and 8.0 g of polyvidone 17 PF and 2.0 g of ethylcellulose are dissolved in 60 ml of dichloromethane. 5.0 g of pantoprazole sodium sesquihydrate are suspended in the solution. The suspension is spray-dried in a laboratory spray-dryer (Büchi Mini Spray Dryer B191). Spray conditions: drying gas nitrogen, inlet temperature 52°C; pump output 12%. A white, free-flowing powder is obtained.

Example 5

5.0 g of β -sitosterol, 8.0 g of polyvidone 17 PF and 1.0 g of ethylcellulose are dissolved in 60 ml of dichloromethane. 5.0 g of pantoprazole sodium sesquihydrate are suspended in the solution. The suspension is spray-dried in a laboratory spray-dryer (Büchi Mini Spray Dryer B191). Spray conditions: drying gas nitrogen, inlet temperature 52°C; pump output 12%. A white, free-flowing powder is obtained.

The preparations obtained according to Examples 1 to 5 have a particle size in the range 10-40 μm . By variation of the spraying conditions, it is possible, for example, to obtain larger or smaller particles.

Production of the preparations by spray-congealing

Example 6

100 g of cetyl alcohol are heated to 65°C. 50 g of pantoprazole sodium sesquihydrate are slowly added. The mixture is stirred until a homogeneous suspension is obtained and subsequently sprayed through a nozzle in a spray dryer.

Example 7

80 g of stearyl alcohol and 10 g of ethylcellulose are heated to 70°C and stirred until a clear solution is obtained. 40 g of pantoprazole sodium sesquihydrate are added and stirred. The homogeneous suspension is spray-congealed in a spray dryer.

Preparation of the suppositories

Example A

194.7 g of suppository base (Adeps solidus/neutralis) are fused to give a clear mass at 40-45°C. After cooling the mass to 39-40°C, the preparation obtained in Example 1 (15.3 g) is introduced homogeneously using a stirrer. The suspension obtained is cooled to 37-38°C and cast into suppositories of 2.1 g each.

Example B

193.8 g of suppository base (Adeps solidus/neutralis) are fused to give a clear mass at 40-45°C. After cooling the mass to 39-40°C, the preparation obtained in Example 3 (16.2 g) is introduced homogeneously using a stirrer. The suspension obtained is cooled to 37-38°C and cast into suppositories of 2.1 g each.

Example C

192.0 g of suppository base (Adeps solidus/neutralis) are fused to give a clear mass at 40-45°C. After cooling the mass to 39-40°C, the preparation obtained in Example 4 (18.0 g) is introduced homogeneously using a stirrer. The suspension obtained is cooled to 37-38°C and cast into suppositories of 2.1 g each.

Example D

192.9 g of suppository base (Adeps solidus/neutralis) are fused to give a clear mass at 40-45°C. After cooling the mass to 39-40°C, the preparation obtained in Example 5 (17.1 g) is introduced homogeneously using a stirrer. The suspension obtained is cooled to 37-38°C and cast into suppositories of 2.1 g each.

The suppositories obtained according to Examples A to D in each case contain 45.6 mg of pantoprazole sodium sesquihydrate.

Stability of the suppositories

Samples of the suppositories obtained according to Examples A, B, C and D were stored at 30°C. After storage for 4 weeks, the suppositories were unchanged. No discoloration was detected. Suppositories in which the active compound was incorporated directly showed a black discoloration after storage for 4 weeks under identical conditions.

Patent Claims

1. A suppository for acid-labile active compounds, comprising at least one pharmaceutical auxiliary and a plurality of individual active compound units, wherein the acid-labile active compound in the individual active compound units is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.
2. The suppository as claimed in claim 1, wherein the acid-labile active compound in the individual active compound units is surrounded by a mixture of at least one sterol and at least one polymer.
3. The suppository as claimed in claim 1, wherein the acid-labile active compound is an acid-labile proton pump inhibitor.
4. The suppository as claimed in claim 1, wherein the acid-labile proton pump inhibitor is pantoprazole, esomeprazole, omeprazole, lansoprazole or rabeprazole.
5. The suppository as claimed in claim 1, wherein the acid-labile proton pump inhibitor is pantoprazole sodium sesquihydrate.
6. The suppository as claimed in claim 1, wherein the sterol is cholesterol, lanosterol, ergosterol, stigmasterol, sitosterol, brassicasterol, campesterol or mixtures thereof.
7. The suppository as claimed in claim 1, wherein the polymer is polyvidone, vinylpyrrolidone/vinyl acetate copolymer, polyvinyl acetate, methylcellulose, ethylcellulose, hydroxypropylcellulose, cellulose ester or mixtures thereof.
8. The suppository as claimed in claim 1, wherein the fatty alcohol is cetyl alcohol, myristyl alcohol, stearyl alcohol or mixtures thereof.
9. The suppository as claimed in claim 1, wherein the pharmaceutical auxiliary is hard fat (Adeps neutralis or Adeps solidus).
10. A process for the production of a suppository as claimed in claim 1, wherein the individual active compound units are introduced into a suitable suppository base and brought into a form suitable for the administration of suppositories.
11. An active compound unit comprising an acid-labile active compound, wherein the acid-labile

active compound is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.

12. A process for the production of an active compound unit according to claim 11, wherein an acid-labile active compound is surrounded by a mixture of at least one sterol and at least one polymer, characterized in that at least one sterol and at least one polymer are dissolved in a suitable solvent, the acid-labile active compound is suspended therein and the suspension obtained is subjected to spray-drying.

13. A process for the production of an active compound unit according to claim 11, wherein an acid-labile active compound is surrounded by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol, characterized in that the fatty alcohol is fused, if desired the polymer and/or the sterol are dissolved therein, the acid-labile active compound is suspended therein and the suspension obtained is subjected to spray-congealing.

14. An active compound unit according to claim 11, wherein the acid-labile active compound is pantoprazole sodium sesquihydrate.

15. An active compound unit according to claim 11, wherein the sterol is cholesterol, lanosterol, ergosterol, stigmasterol, sitosterol, brassicasterol, campesterol or mixtures thereof.

16. An active compound unit according to claim 11, wherein the polymer is polyvidone, vinylpyrrolidone/vinyl acetate copolymer, polyvinyl acetate, methylcellulose, ethylcellulose, hydroxypropylcellulose, cellulose ester or mixtures thereof.

17. An active compound unit according to claim 11, wherein the fatty alcohol is cetyl alcohol, myristyl alcohol, stearyl alcohol or mixtures thereof.

18. Preparation comprising an acid-labile active compound, at least one sterol and at least one polymer obtainable by spray-drying of a suspension of the acid-labile active compound in a solution of the sterol and the polymer in a suitable solvent.

19. Preparation comprising an acid-labile active compound, at least one fatty alcohol or a mixture of at least one fatty alcohol and at least one polymer and/or sterol obtainable by spray-congealing of a suspension of the acid-labile compound in a solution, if desired, of the polymer and/or sterol in the fatty alcohol.

INTERNATIONAL SEARCH REPORT

Intern. Appl. No.

PCT/EP 98/07946

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K9/02 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 645 140 A (TAKEDA CHEMICAL INDUSTRIES) 29 March 1995 see the whole document	1,3-5, 7-10,18, 19
P,X	WO 98 52564 A (CIPLA LIMITED) 26 November 1998 see claims 1-4,9,10,16-18	11,16,17

☐ Further documents are listed in the continuation of box C.

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 98/07946

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/44, 9/10, A61P 1/04	A1	(11) International Publication Number: WO 00/50038 (43) International Publication Date: 31 August 2000 (31.08.00)
(21) International Application Number: PCT/US00/04170 (22) International Filing Date: 18 February 2000 (18.02.00) (30) Priority Data: 60/121,253 23 February 1999 (23.02.99) US (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): FREEHAUF, Keith [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US). (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING PROTON PUMP INHIBITORS		
(57) Abstract The present invention is concerned with an oral pharmaceutical formulation containing a proton pump inhibitor (PPI) which is suitable for the treatment of gastric acid related diseases in man and animals. More specifically, the composition is a paste, and is particularly suitable for delivery of a proton pump inhibitor to horses.		

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TITLE OF THE INVENTION**PHARMACEUTICAL COMPOSITION CONTAINING PROTON PUMP
INHIBITORS****5 SUMMARY OF THE INVENTION**

The present invention relates to an improved oral paste formulation of omeprazole.

BACKGROUND OF THE INVENTION

10 Omeprazole is a potent inhibitors of gastric acid secretion that acts by inhibiting H^+K^+ -ATPase, the enzyme involved in the final step of hydrogen ion production in the parietal cells, and has been used in the treatment of gastric acid related diseases, such as gastric and duodenal ulcers, in humans. Peptic ulcers are common also in some animals, particularly in horses. Although the etiology of gastro-
15 duodenal ulcers in horses has not been ascertained, it appears that stress plays an important roles in some cases.

Omeprazole is highly acid labile and hence oral formulations are enteric-coated. Enteric coated formulations are expensive and time consuming to manufacture, and requires elaborate technology and equipment. Another disadvantage
20 of enteric coated formulation is its moisture sensitivity.

WO94/25070 discloses oral composition containing a proton pump inhibitor in the form of enteric coated dry particles mixed with a dry gelling agent, the mixture may then be made into a paste-like gel prior to administration. The composition therefore requires enteric coating, with the afore-mentioned
25 disadvantages associated with such formulation. Furthermore, because such a moist gel is not stable during long-term storage at room temperature it cannot be manufactured and sold as a ready-to-use formulation, rather it must be prepared ex tempore at the time of administration, making it inconvenient to use.

US Patent 5,708,017 describes paste formulations of proton-pump
30 inhibitors comprising a proton-pump inhibitor, a thickening agent, a basifying agent and a hydrophobic oily liquid vehicle.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an improved paste formulation of omeprazole comprising:

- (a) about 1% to about 60% w/w of omeprazole,
- 5 (b) about 0.1% to about 2% w/w of two to four basifying agents,
- (c) about 1% to about 3% w/w of a thickening agent, and
- (d) about 30% to about 95% w/w of a hydrophobic oily liquid vehicle comprising

- (i) a vegetable oil and
- 10 (ii) triglycerides of medium chain fatty acids or propylene glycol diesters of medium chain fatty acids.

Omeprazole is disclosed in US Patent 4,255,432. The amount of omeprazole in the present invention is not particularly critical so long as the drug product remains a semi-solid preparation; generally up to about 60% w/w of omeprazole can be tolerated. Preferably the amount of omeprazole is about 50 % w/w or less, and more preferably from about 30 to about 40 % w/w.

Suitable basifying agents are for example pharmaceutically acceptable amine bases such as monoethanolamine, diethanolamine, triethanolamine, or salts of carboxylic acids such as sodium acetate, sodium citrate, potassium sorbate, sodium stearate and the like. Preferably one of the basifying agent is potassium sorbate, and one or two other basifying agents may be selected from an amine base such as monoethanolamine and a carboxylic acid salt such as sodium stearate. The basifying agents are present in an amount sufficient to provide a non-acidic environment for the acid-labile omeprazole; typically, the total amount of basifying agents is from about 0.1 to about 2 % w/w, and preferably from about 1 to about 1.5 % w/w.

The thickening agent may be any pharmaceutically acceptable thickener that are insoluble or practically insoluble in water; examples include silicone dioxide, waxes such as castor wax or hydrogenated castor oil, paraffin, cetostearyl alcohol, and the like. The preferred hydrophobic thickener is hydrogenated castor oil. The amount of thickening agent is approximately 0.5% to 10% w/w of the final composition; preferably, it is about 1 to 2 % w/w.

The hydrophobic oily liquid vehicle comprises (i) a vegetable oil and (ii) triglycerides of medium chain fatty acids or propylene glycol diesters of medium

chain fatty acids. Examples of vegetable oil include almond oil, cottonseed oil, olive oil, peanut oil, safflower oil, sesame oil, and soybean oil. The preferred vegetable oil is sesame oil. Medium chain fatty acids are those having carbon chain lengths of from eight to twelve; preferably the fatty acids are saturated fatty acids. Preferred

5 triglycerides and propylene glycol diesters are capric/caprylic triglycerides and propylene glycol caprate/caprylate (also referred to as propylene glycol octanoate decanoate). Capric/caprylic triglycerides and propylene glycol caprate/caprylate are commercially available products such as those marketed under the Miglyol®

10 tradename (Huls America, Inc., New Jersey). The more preferred hydrophobic oily liquid vehicle comprises sesame oil and propylene glycol caprate/caprylate (such as Miglyol® 840). The hydrophobic vehicle is present at approximately 30% to 95% w/w, depending on the amount of other excipients in the paste. Preferably the hydrophobic vehicle is present at about 50 to about 80% w/w. In the hydrophobic vehicle the ratio of the vegetable oil to the triglyceride may range from about 1:3 to

15 about 5:1; preferably about 1:1 to about 2:1.

The present composition may include additional ingredients commonly used in the formulation of human and veterinary medicines. For example, flavoring agents such as caramel, carrot, apple, cinnamon and sausage flavors; coloring agents such as iron oxide, titanium dioxide, aluminum lakes; sweeteners such as sugar,

20 sodium saccharin; preservatives such as parabens; antioxidants such as BHT, BHA; dispersants such as calcium stearate, and viscosity regulating agents such as white wax or synthetic waxes such as glyceryl trihehenate, glyceryl trimyristate, hydrogenated coco-glycerides can be added.

The composition of the present invention may be prepared by

25 dispersing omeprazole in powder form in the hydrophobic liquid vehicle containing any other excipients except the thickening agent. The thickening agent is then added to the mixture and mixed to achieve the desired consistency. The composition of the present invention may also be prepared by dispersing the excipients in the hydrophobic oily liquid vehicle, followed by addition of the thickening agent, and if

30 needed additional vegetable oil to achieve the desired consistency; to the resultant mixture is added omeprazole in powder form and the entire mixture is mixed well to disperse the omeprazole. The paste formulation thus obtained may be used to fill

dosing syringes, which may be used directly to administer the active drug to an animal in need of treatment.

5 The omeprazole paste formulations of the present invention have improved properties over previously described omeprazole paste formulations. The present formulations have better chemical and physical stability profiles, and provide higher drug bioavailability.

10 The composition of the present invention are useful in the treatment of peptic ulcer diseases in humans or animals. It can be used to deliver omeprazole orally for systemic activity in animals. The composition can also be used for the delivery of omeprazole in human with difficulty of swallowing solid dosage forms such as enteric coated tablets and capsules. The composition may be administered directly into the mouth of an animal, such as a horse, in need of anti-ulcer therapy; preferably a paste dosing syringe is used to facilitate drug administration. The consistency of this paste is such that it can not easily drip out or be expelled once it is deposited on the dorsal part of the animal's tongue. The paste is practically free of air bubbles which enhances dosing accuracy. Another advantage of this formulation is that individualized doses can be administered.

15 The amount of the composition to be administered may vary according to the particular animal species to be treated, the severity of the disease, the physical condition of the afflicted animal, and other factors. A physician or veterinarian skilled in the art of ulcer treatment may readily determined the proper dosage for the specific host under treatment. In general, a dose range of from about 0.2 mg/kg to about 20 mg/kg may be used.

25 The following example is provided to more fully illustrate the invention, and shall not be construed as limiting the scope of the invention in any manner.

EXAMPLE 1

<u>Component</u>	<u>Percent w/w</u>
omeprazole base	37.0
potassium sorbate	0.20
sodium stearate	0.10
calcium stearate	1.0
monoethanolamine	0.10
yellow iron oxide	0.20
cinnamon oil	0.30
hydrogenated castor oil	1.25
propylene glycol octanoate decanoate	25.0
sesame oil	qs

5 Potassium sorbate (0.50 kg), calcium stearate (2.50 kg), sodium stearate (0.25 kg), and yellow iron oxide (0.50 kg) are added to a double cone blender and mixed to disperse powders. The resultant powder is passed through a 60 mesh screen and milled at high speed. This milled powder preblend is collected in a polyethylene bag for use in paste manufacturing.

10 In a suitably sized vertical screw semi-solid paste mixer are added propylene glycol octanoate decanoate (62.5 kg) and sesame oil (37.5 kg). The temperature of the liquid mixture is adjusted to below approximately 25°C, if necessary, and the mixing screw is turned on. With the lumpbreaker on, the milled powder preblend, monoethanolamine (0.25 kg), and cinnamon oil (0.75 kg) are added to the mixer. Next, hydrogenated castor oil (3.13 kg) is added to the mixer, and
15 mixing is until the product temperature reaches 50 ± 5°C. The mixing screw and the lumpbreaker are stopped and the batch in the vessel is held for 30±5 minutes to assure completion of the gelling process.

20 With cooling water on, the remaining sesame oil (49.6 kg) is added to the mixer. The mixing screw and lumpbreaker are turned on for approximately two minutes to disperse the materials and then stopped. Omeprazole powder (92.5 kg) is added to the mixer in 8 -10 portions; after addition of each portion the mixer is turned on for a period sufficient to wet most of the powder and then turned off for the

addition of the next portion. After all the omeprazole has been added, mixing is continued for an additional 10 minutes to fully disperse the omeprazole; then the lumpbreaker is turned on and mixing continues for an additional 10 minutes to assure complete homogeneity. The resultant paste is used for packaging into syringes.

WHAT IS CLAIMED IS:

1. A pharmaceutical formulation for oral administration
comprising:
 - (a) about 1% to about 60% w/w of omeprazole,
 - (b) about 0.1% to about 2% w/w of two to four basifying agents,
 - (c) about 1% to about 3% w/w of a thickening agent, and
 - (d) a hydrophobic oily liquid vehicle comprising
 - (i) a vegetable oil and
 - (ii) triglycerides of medium chain fatty acids or propylene glycol diesters of medium chain fatty acids.
2. A composition of Claim 1 wherein said thickening agent is hydrogenated castor oil.
3. A composition of Claim 1 wherein said hydrophobic liquid vehicle comprises propylene glycol caprate/caprylate and a vegetable oil.
4. A composition of Claim 1 wherein said hydrophobic liquid vehicle comprises sesame oil and triglycerides of medium chain fatty acids or propylene glycol diesters of medium chain fatty acids.
5. A composition of Claim 1 wherein said hydrophobic liquid vehicle comprises propylene glycol caprate/caprylate and sesame oil.
6. A composition of Claim 1 wherein one of the basifying agents is potassium sorbate.
7. A composition of Claim 1 wherein the basifying agents are potassium sorbate, sodium stearate and monoethanolamine.

8. A composition of Claim 1 wherein the amount of omeprazole is about 30 to about 40 % w/w.

9. A composition of Claim 1 wherein the total amount of
5 basifying agents is from about 1 to about 1.5% w/w.

10. A composition of Claim 1 wherein the amount of the hydrophobic oily liquid vehicle is about 30% to 90% w/w.

10 11. A composition of Claim 1 wherein the amount of the hydrophobic oily liquid vehicle is about 50% to 80% w/w.

INTERNATIONAL SEARCH REPORT

Int. Appl. No.

PCT/US 00/04170

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/44 A61K9/10 A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 708 017 A (DAVE KAUSHIK J ET AL) 13 January 1998 (1998-01-13) cited in the application column 1, line 46 - line 65 column 3, line 51 - column 4, line 29 column 5 - column 6; examples 1-5 claims 1-8	1,2,4,6, 8-11
T	"Oral dosage form for new animal drugs; Omeprazole." FEDERAL REGISTER, vol. 64, no. 72, 1999, pages 18572-18573, XP000929106 page 18572, column 3 - page 18573, column 1	1-11



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Date of the actual completion of the international search

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Muller, S

INTERNATIONAL SEARCH REPORT

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International Application No

PCT/US 00/04170

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		SK 135097 A	03-06-1998
		WO 9631213 A	10-10-1996
		ZA 9602657 A	09-10-1996



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/44, 9/50	A1	(11) International Publication Number: WO 99/29320 (43) International Publication Date: 17 June 1999 (17.06.99)
(21) International Application Number: PCT/EP98/08036 (22) International Filing Date: 8 December 1998 (08.12.98) (30) Priority Data: 197 54 324.3 8 December 1997 (08.12.97) DE 198 22 549.0 20 May 1998 (20.05.98) DE (71) Applicant (for all designated States except US): BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH [DE/DE]; Byk-Gulden-Strasse 2, D-78467 Konstanz (DE). (72) Inventors; and (75) Inventors/Applicants (for US only): LINDER, Rudolf [AT/DE]; Felchengang 22, D-78464 Konstanz (DE). DIETRICH, Rango [DE/DE]; Im Tiergarten 16, D-78465 Konstanz (DE). (74) Common Representative: BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH; Byk-Gulden-Strasse 2, D-78467 Konstanz (DE).		(81) Designated States: AL, AU, BA, BG, BR, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, JP, KR, LT, LV, MK, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, VN, YU, ZW, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: NOVEL ADMINISTRATION FORM COMPRISING AN ACID-LABILE ACTIVE COMPOUND		
(57) Abstract <p>Novel administration form for acid-labile active compounds are described. The novel administration forms have no enteric layers and are suitable for oral administration.</p>		

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Novel administration form comprising an acid-labile active compound**Technical field**

The present invention relates to the field of pharmaceutical technology and describes a novel administration form comprising an acid-labile active compound, in particular an acid-labile proton pump inhibitor. The novel administration form is suitable for oral administration. Furthermore, the invention also relates to a process for the production of the administration form and preparations which can be used for the production of the administration form.

Prior art

It is generally known to coat oral administration forms, e.g. tablets or pellets, which contain an acid-labile active compound, with an enteric coating which is rapidly dissolved in the alkaline medium of the intestine after gastric passage. An example of such acid-labile active compounds is acid-labile proton pump inhibitors (H^+/K^+ ATPase inhibitors), in particular pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, such as are disclosed, for example, in EP-A-0 005 129, EP-A-0 166 287, EP-A-0 174 726 and EP-A-0 268 956. On account of their H^+/K^+ ATPase-inhibiting action, these are of great importance in the therapy of diseases which result from increased gastric acid secretion. Examples of already commercially available active compounds from this group are 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methylsulfinyl]-1H-benzimidazole (INN: omeprazole), 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)-methylsulfinyl]-1H-benzimidazole (INN: pantoprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]-methylsulfinyl-1H-benzimidazole (INN: lansoprazole) and 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl]-methylsulfinyl]-1H-benzimidazole (INN: rabeprazole).

Because of their strong tendency to decompose in a neutral and, in particular, acidic environment, strongly colored decomposition products also being formed, it is also necessary in this case for oral preparations to protect the active compounds from the action of acids and moisture and destruction by undesired interaction with pharmaceutical auxiliaries. In the case of the highly acid-labile pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, it is moreover necessary to process these in the tablet core or in pellets in the form of their alkaline salts, for example as sodium salts, or together with alkaline substances. Since the substances possible for enteric coatings are those having free carboxyl groups, the problem results that the enteric coating, because of the alkaline medium in the interior, begins to dis-

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solve or is even dissolved from the inside out and the free carboxyl groups promote the decomposition of the active compounds. It is therefore necessary to provide an insulating intermediate layer (subcoating) between the enteric coating and the alkaline tablet core or pellet. In EP-A-0 244 380, it is proposed to coat cores which contain the active compound together with alkaline compounds or as an alkaline salt with at least one layer of nonacidic, inert pharmaceutically acceptable substances, which is soluble in water or rapidly disintegrates in water, before the enteric layer is applied. The intermediate layer or intermediate layers act as pH-buffering zones in which the hydrogen ions diffusing in from outside can react with the hydroxyl ions diffusing out of the alkaline core. In order to increase the buffer capacity of the intermediate layer, it is proposed to incorporate buffer substances into the intermediate layer(s). In practice, it is possible by this process to obtain preparations which are stable to a certain extent. However, relatively thick intermediate layers are needed to avoid the unattractive discolorations which occur even in the case of only slight decomposition. Additionally, a considerable effort has to be made during preparation to avoid traces of moisture.

In EP-A-0 519 365, a formulation for the active compound pantoprazole on the principle of the alkaline core coated with a water-soluble intermediate layer and an enteric layer is proposed, in which an improved stability is achieved by use of polyvinylpyrrolidone and/or hydroxypropylmethylcellulose as a binder for the alkaline core.

In EP-A-0 342 522, a formulation for acid-sensitive benzimidazoles is disclosed in which between the alkaline core and the enteric coating is situated an intermediate layer which is composed of an only slightly water-soluble film-forming material, such as ethylcellulose or polyvinyl acetate, and a slightly water-soluble fine-grain inorganic or organic material suspended therein, such as, for example, magnesium oxide, silicon oxide or sucrose fatty acid esters.

EP-A-0 277 741 describes spherical grains or granules having a core which is coated with spray powder which contains low-substituted hydroxypropyl-cellulose and a benzimidazole compound having antiulcer activity. These grains can be coated with an enteric coating agent.

WO96/01623, WO96/01624 and WO96/01625 describe an administration form for acid-labile H^+/K^+ ATPase inhibitors in which active compound pellets together with tablet auxiliaries are compressed to give a tablet. The pellets consist of cores which contain the acid-labile H^+/K^+ ATPase inhibitor together with alkaline compounds or as an alkaline salt. The cores of the pellets are coated with one or more layers, at least one layer having enteric properties. The enteric layer must in this case be mechanically constituted such that on compression to give tablets the acid resistance of the pellets is not adversely affected. It is mentioned that the preparation of the cores of the pellets can be effected by spray drying.

WO97/25030 describes the processing of the abovementioned pellets to give an effervescent tablet.

As the abovementioned prior art shows, the preparation of oral administration forms for acid-labile active compounds requires technically complicated processes.

Description of the invention

It is an object of the present invention to provide a novel oral administration form for acid-labile active compounds in which the acid-labile active compound does not have to be protected by an enteric coating and which can be prepared without great technical effort.

It has now surprisingly been found that this object can be achieved by an administration form which comprises a plurality of individual active compound units.

The invention relates to an oral administration form comprising an acid-labile active compound and pharmaceutical auxiliaries, wherein the auxiliaries are not suitable for the formation of enteric layers (enteric coating). Preferably the active compound in the oral administration form is present in the form of a plurality of individual active compound units.

Further subjects follow from the patent claims.

The plurality of individual active compound units in the sense of the invention is a plurality of individual units (multiple individual units) in which at least one active compound particle is present. Preferably in the individual units, the active compound is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.

Further subject of the invention is an oral administration form for acid-labile active compounds, comprising at least one pharmaceutical auxiliary and a plurality of individual active compound units, wherein the acid-labile active compound in the individual active compound units is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.

A preferred subject of the invention is an oral administration form for acid-labile active compounds, comprising at least one pharmaceutical auxiliary and a plurality of individual active compound units, wherein the acid-labile active compound in the individual active compound units is surrounded by a mixture of at least one sterol and at least one polymer.

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Further subject of the invention is an active compound unit comprising an acid-labile active compound, wherein the acid-labile active compound is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.

The particle size of the individual units is advantageously less than 200 μm , preferably less than 100 μm . Preferably, the particle size is in the range from 2 μm to 50 μm , particularly preferably in the range from 4 μm to 20 μm .

Acid-labile active compounds in the sense of the present invention are, in particular, acid-labile proton pump inhibitors.

Acid-labile proton pump inhibitors (H^+/K^+ ATPase inhibitors) which may be mentioned in the sense of the present invention are, in particular, substituted pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, such as are disclosed, for example, in EP-A-0 005 129, EP-A-0 166 287, EP-A-0 174 726, EP-A-0 184 322, EP-A-0 261 478 and EP-A-0 268 956. Preferably, mention may be made here of 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: omeprazole), 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: pantoprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: lansoprazole) and 2-[[4-(3-methoxypropoxy)-3-methylpyridin-2-yl)methylsulfinyl]-1H-benzimidazole (INN: rabeprazole).

Further acid-labile proton pump inhibitors, for example substituted phenylmethylsulfinyl-1H-benzimidazoles, cycloheptapyridin-9-ylsulfinyl-1H-benzimidazoles or pyridin-2-ylmethylsulfinylthienimidazoles are disclosed in DE-A-35 31 487, EP-A-0 434 999 or EP-A-0 234 485. Mention may be made by way of example of 2-[2-(N-isobutyl-N-methylamino)benzylsulfinyl]benzimidazole (INN: leminoprazole) and 2-(4-methoxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ylsulfinyl)-1H-benzimidazole (INN: nepaprazole).

The acid-labile proton pump inhibitors are chiral compounds. The term acid-labile proton pump inhibitor also includes the pure enantiomers of the acid-labile proton pump inhibitors and their mixtures in any mixing ratio including the racemates. Enantiomerically pure acid-labile proton pump inhibitors are disclosed, for example, in WO92/08716. Esomeprazole may be mentioned by way of example.

The acid-labile proton pump inhibitors are present here as such or preferably in the form of their salts with bases. Examples of salts with bases which may be mentioned are sodium, potassium, magnesium or calcium salts. If desired, the salts of the acid-labile proton pump inhibitors with bases can also

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be present in hydrate form. Such a hydrate of the salt of an acid-labile proton pump inhibitor with a base is disclosed, for example, in WO 91/19710.

Particularly preferred acid-labile proton pump inhibitors which may be mentioned are pantoprazole sodium and pantoprazole sodium sesquihydrate (= pantoprazole sodium \times 1.5 H₂O).

The sterol is preferably a phytosterol or a zoosterol. Phytosterols which may be mentioned by way of example are ergosterol, stigmasterol, sitosterol, brassicasterol and campesterol. Zoosterols which may be mentioned by way of example are cholesterol and lanosterol. If desired, mixtures of sterols can also be present.

The polymer is preferably a polymer having nonacidic groups. Polymers which may be mentioned by way of example are polyvidone (e.g. Kollidon 17, 30 and 90 from BASF), vinylpyrrolidone/vinyl acetate copolymer and polyvinyl acetate. Cellulose ethers such as, for example, methylcellulose, ethylcellulose (Ethocel) and hydroxypropylmethylcellulose and cellulose esters (e.g. cellulose acetate phthalate) may furthermore be mentioned. If desired, mixtures of polymers can also be present.

The fatty alcohol is preferably a linear, saturated or unsaturated primary alcohol having 10-30 carbon atoms. Fatty alcohols which may be mentioned by way of example are cetyl alcohol, myristyl alcohol or stearyl alcohol. If desired, mixtures of fatty alcohols can also be present.

The amount (in % by weight) of active compound in the individual active compound unit is advantageously 1-90%. In case of units in which at least one active compound particle is present, surrounded by a mixture of at least one sterol and at least one polymer the amounts of sterol and of polymer are in each case advantageously 5-80%. Preferably, the amount of active compound is 10-50%, the amount of sterol is 10-40% and the amount of polymer is 10-50%.

In case of units in which at least one active compound particle is present, surrounded by at least one fatty alcohol, preferably the amount of active compound is 2-70 % and the amount of fatty alcohol is 30-98 %.

In case of units in which at least one active compound particle is present, surrounded by at least one fatty alcohol and at least one sterol, preferably the amount of active compound is 2-70 %, the amount of fatty alcohol is 20-90 % and the amount of sterol is 8-50 %.

In case of units in which at least one active compound particle is present, surrounded by at least one fatty alcohol and at least one polymer, preferably the amount of active compound is 10-60 %, the amount of fatty alcohol is 10-50 % and the amount of polymer is 10-40 %.

In case of units in which at least one active compound particle is present, surrounded by at least one fatty alcohol, at least one polymer and at least one sterol, preferably the amount of active ingredient is 2-70 %, the amount of fatty alcohol is 20-85 %, the amount of polymer is 2-25 % and the amount of sterol is 10-50 %.

It is possible for the person skilled in the art, on account of his/her expert knowledge, to select the best suited sterols and polymers depending on the active compound.

The individual active compound units can be prepared, for example, by spray-congealing (spray solidification) or preferably by spray-drying. Preferably spray-drying is used for the preparation of individual active compound units in which the active compound is surrounded by a mixture of at least one sterol and at least one polymer. Spray-drying takes place from a suitable solvent. Suitable solvents for the spray drying are preferably those in which the sterol and the polymer are soluble, while the active compound is insoluble. Suitable solvents can also be solvent mixtures.

If an acid-labile proton pump inhibitor, in particular a substituted pyridin-2-ylmethylsulfinyl-1H-benzimidazole, is employed as an active compound, the suitable solvents are, for example, hydrocarbons, chlorinated hydrocarbons and ethyl acetate. Hydrocarbons which may be mentioned are, in particular, linear or branched alkanes or alternatively cycloalkanes. Examples of linear alkanes are pentane, hexane and heptane. Examples of branched alkanes which may be mentioned are 2-methylpentane and 3-methylpentane. Examples of cycloalkanes which may be mentioned are cyclohexane and cyclopentane. If desired, mixtures of the hydrocarbons such as, for example, petroleum ether can also be employed. As a chlorinated hydrocarbon, chloroform and preferably dichloromethane may be mentioned.

On account of his/her expert knowledge in the field of spray drying and, if necessary, by means of customary tests, it is possible for the person skilled in the art, depending on the active compound employed, to select the best suited sterols, polymers and solvents.

For spray-drying, the sterol and the polymer are dissolved in the suitable solvent and the active compound is suspended therein. If desired, the active compound can also be suspended first and the sterol and polymer then dissolved. The suspension obtained is then sprayed in a spray drier.

Spray drying is carried out in a manner known per se. A detailed presentation of this technique is found in K. Masters, Spray Drying Handbook, 5th edition 1991, and J. Broadhead, S. K. Edmond Ronan, C. T. Rhodes, The Spray Drying of Pharmaceuticals, Drug Dev. Ind. Pharm. 18, 1169 (1992). The principle of spray drying consists in breaking down a solution or suspension of the product to be

dried into fine droplets and drying it using a hot stream of gas. The solid components remaining after evaporation of the solvent are separated off from the stream of gas by means of a cyclone and/or by a filter unit and collected.

Possible drying gases are, in particular, air and preferably nitrogen. The gas inlet temperature depends on the solvent.

Further subject of the invention is a preparation comprising an acid-labile active compound, at least one sterol and at least one polymer obtainable by spray-drying of a suspension of the acid-labile active compound in a solution of the sterol and the polymer in a suitable solvent.

Preferably spray-congealing is used for the preparation of individual active compound units in which the active compound is surrounded by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.

For spray-congealing the fatty alcohol is fused and, if desired, the polymer and/or the sterol are dissolved therein to give a homogeneous solution. The active compound is then suspended in the solution. The suspension obtained is then sprayed in a spray-dryer.

Spray-congealing is carried out in a manner known per se. A detailed presentation of this technique is found for example in P.B. Deasy, Microencapsulation and Related Drug Process (1984).

Further subject of the invention is a preparation comprising an acid-labile active compound, at least one fatty alcohol or a mixture of at least one fatty alcohol and at least one polymer and/or sterol obtainable by spray-congealing of a suspension of the acid-labile compound in a solution, if desired, of the polymer and/or sterol in the fatty alcohol.

The particle size of the active compound used in the spray-drying or spray-congealing process is advantageously less than 100 μm , preferably less than 40 μm . Preferably, the particle size is in the range from 1-20 μm , particularly preferably in the range from 3-15 μm . Such particle size of the active compound for example can be achieved by milling the active compound in a suitable mill.

The individual active compound units, subsequently also designated as preparations, can then serve as a base for the production of the oral administration forms according to the invention. Examples of oral administration forms according to the invention to which the preparations can be processed are solutions, suspensions, emulsions, gels, tablets, effervescent tablets, powder in sachets, coated tablets or capsules. The person skilled in the art is familiar on the basis of his/her expert knowledge with auxiliaries which are suitable for the desired administration form. For the administration forms, it is

surprisingly possible to dispense with the enteric coating and in spite of this to achieve a therapeutic action on oral administration.

The oral administration forms according to the invention contain the acid-labile active compound in a dose customary for the treatment of the appropriate disorder. The oral administration forms according to the invention comprising acid-labile proton pump inhibitors are suitable for the treatment and prevention of all diseases for the treatment or prevention of which pyridin-2ylmethylsulfinyl-1H-benzimidazoles are employed. In particular the oral administration forms according to the invention can be employed in the treatment of diseases of the stomach. Thus, the oral administration forms according to the invention contain between 1 and 500 mg, preferably between 5 and 60 mg, of an acid-labile proton pump inhibitor. Examples which may be mentioned are tablets or capsules which contain 10, 20, 40 or 50 mg of pantoprazole sodium sesquihydrate. The daily dose (e.g. 40 mg of active compound) can in this case be administered in the form of a single administration or in several administrations using the oral administration forms according to the invention.

The oral administration forms comprising acid labile compounds according to the invention can also be combined with other active compounds, either in fixed or in free combination. Fixed combination in this connection relates to an administration form wherein all active compounds are present in a single dosage unit. Free combination in this connection relates to an administration form, wherein the active compounds are present in separated dosage units. In connection with oral administration forms comprising acid-labile proton pump inhibitors a combination with antimicrobially active compounds or NSAIDs (non steroidal anti inflammatory drugs) may be mentioned. Particularly mention may be made of a combination with antimicrobially active compounds which can be used in the control of *Helicobacter pylori* (*H. pylori*).

Examples of suitable antimicrobially-active ingredients (active against *Helicobacter pylori*) are enumerated in European Patent Application EP-A-282131. These active ingredients include, for example, bismuth salts (such as bismuth subcitrate or bismuth subsalicylate), sulfonamides, nitrofurans (such as nitrofurazone, nitrofurantoin or furazolidone), metronidazole, tinidazole, nimorazole or antibiotics. Examples of antibiotics which may be mentioned in this connection are, arranged according to particular classes of active ingredient: aminoglycosides, such as gentamicin, neomycin, kanamycin, amikacin or streptomycin; macrolides, such as erythromycin, azithromycin, clarithromycin, clindamycin or rifampicin; penicillins, such as penicillin G, penicillin V, ampicillin, mezlocillin or amoxicillin; polypeptides, such as bacitracin or polymyxin; tetracyclines, such as tetracycline, chlorotetracycline, oxytetracycline, minocycline or doxycycline; carbapenems, such as imipenem, loracarbef, meropenem or panipenem; cephalosporins, such as cefalexin, cefoxitin, cefuroxime axetil, cefotaxime, cefpodoxime proxetil, cefaclor, cefadroxil or cephalothin; gyrase inhibitors, such as ciprofloxacin, norfloxacin, ofloxacin or pefloxacin; or other different antibiotics, such as chloramphenicol. Particularly worthy of men-

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tion in this connection is also the combination of a plurality of antimicrobially-active ingredients, for example the combination of a bismuth salt and/or tetracycline with metronidazole, or the combination of amoxicillin or clarithromycin with metronidazole and amoxicillin with clarithromycin.

Particularly worthy of mention in this connection is also administration of a proton pump inhibitor together with a plurality of antimicrobially-active ingredients, for example with the combination of a bismuth salt and/or tetracycline with metronidazole or with the combination of amoxicillin or clarithromycin or with metronidazole.

The preparation of administration forms according to the invention is described by way of example below. The examples below illustrate the invention in greater detail without restricting it.

Production of the preparations by spray-drying**Example 1**

7.0 g of cholesterol and 5.0 g of Ethocel are dissolved in 100 ml of dichloromethane. 5.0 g of pantoprazole sodium sesquihydrate are suspended in the solution. The suspension is spray-dried in a laboratory spray-dryer (Büchi Mini Spray Dryer B191). Spray conditions: drying gas nitrogen, inlet temperature 51°C; pump output 10%. A white, free-flowing powder is obtained.

Example 2

5.0 g of cholesterol and 5.0 g of Kollidon 17 are dissolved in 80 ml of dichloromethane. 5.0 g of omeprazole magnesium are suspended in the solution. The suspension is spray-dried in a laboratory spray-dryer (Büchi Mini Spray Dryer B191). Spray conditions: drying gas nitrogen, inlet temperature 51°C; pump output 10%. A white, free-flowing powder is obtained.

Example 3

5.0 g of cholesterol and 8.0 g of polyvidone 17 PF are dissolved in 60 ml of dichloromethane. 5.0 g of pantoprazole sodium sesquihydrate are suspended in the solution. The suspension is spray-dried in a laboratory spray-dryer (Büchi Mini Spray Dryer B191). Spray conditions: drying gas nitrogen, inlet temperature 52°C; pump output 12%. A white, free-flowing powder is obtained.

Example 4

5.0 g of cholesterol and 8.0 g of polyvidone 17 PF and 2.0 g of ethylcellulose are dissolved in 60 ml of dichloromethane. 5.0 g of pantoprazole sodium sesquihydrate are suspended in the solution. The suspension is spray-dried in a laboratory spray-dryer (Büchi Mini Spray Dryer B191). Spray conditions: drying gas nitrogen, inlet temperature 52°C; pump output 12%. A white, free-flowing powder is obtained.

Example 5

5.0 g of β -sitosterol, 8.0 g of polyvidone 17 PF and 1.0 g of ethylcellulose are dissolved in 60 ml of dichloromethane. 5.0 g of pantoprazole sodium sesquihydrate are suspended in the solution. The suspension is spray-dried in a laboratory spray-dryer (Büchi Mini Spray Dryer B191). Spray conditions:

drying gas nitrogen, inlet temperature 52°C; pump output 12%. A white, free-flowing powder is obtained.

The preparations obtained according to Examples 1 to 5 have a particle size in the range 10-40 µm. By variation of the spraying conditions, it is possible, for example, to obtain larger or smaller particles.

Production of the preparations by spray-congealing

Example 6

100 g of cetyl alcohol are heated to 65°C. 50 g of pantoprazole sodium sesquihydrate are slowly added. The mixture is stirred until a homogeneous suspension is obtained and subsequently sprayed through a nozzle in a spray dryer.

Example 7

80 g of stearyl alcohol and 10 g of ethylcellulose are heated to 70°C and stirred until a clear solution is obtained. 40 g of pantoprazole sodium sesquihydrate are added and stirred. The homogeneous suspension is spray-congealed in a spray dryer.

Preparation of the administration forms

Example A (Granules)

134.7 g of mannitol, 30 g of Kollidon 30 and 20 g of xanthan are mixed dry. The mixture is granulated with water in a fluidized bed granulator. Granules having a particle size of 0.8-1.5 mm are obtained, which are mixed with the preparation (15.3 g) obtained according to Example 1. The mixture thus obtained is filled into sachets or compressed to give tablets - if desired together with further tablet auxiliaries - in a manner known to the person skilled in the art.

Example B

An amount corresponding to 22.6 mg pantoprazole sodium sesquihydrate of the powder formulation as described in Example 5 is mixed with appropriate amounts of lactose. This mixture is flavoured according to individual taste and filled into minibags (Sachets) each containing one individual dose.

The contents of one minibag are dispersed in a glass of tap water under stirring to obtain a suspension for oral intake.

Example C

An amount corresponding to 45.2 mg pantoprazole sodium sesquihydrate of the powder formulation as described in Example 1 is mixed with appropriate amounts of lactose. This mixture is combined with a mixture of citric acid and sodium carbonate. After addition of a suitable lubricant (e.g. sodium stearyl fumarate) and appropriate flavouring the mixture is directly (without further granulation) compressed to effervescent tablets. One tablet is to be thrown into a glass of a water to obtain a drinking suspension after tablet disintegration.

Example D

An amount corresponding to 45.2 mg pantoprazole sodium sesquihydrate of the powder formulation as described in Example 4 is mixed with appropriate amounts of (fast flowing) lactose for improvement of powder flow properties. This mixture is filled into appropriately sized hard gelatine capsules together with suitable concomitant medication like antibiotics (e.g. amoxicillin for *Helicobacter pylori* eradication) or NSAIDs (non steroidal anti inflammatory drugs) in available dosage forms.

Patent Claims

1. An oral administration form for acid-labile active compounds comprising an acid-labile active compound and pharmaceutical auxiliaries, wherein the auxiliaries are not suitable for the formation of enteric layers.
2. An oral administration form as claimed in claim 1, wherein the active compound is present in the form of a plurality of individual active compound units, the units having a particle size less than 200 μm .
3. An oral administration form as claimed in claim 1, wherein the active compound is present in the form of a plurality of individual active compound units, the units having a particle size less than 100 μm .
4. An oral administration form as claimed in claim 1, wherein the active compound is present in the form of a plurality of individual active compound units, the units having a particle size in the range from 4-20 μm .
5. An oral administration form for acid-labile active compounds comprising pharmaceutical auxiliaries and a plurality of individual active compound units, wherein the acid-labile active compound in the individual active compound units is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol.
6. An oral administration form as claimed in claim 5, wherein the acid-labile active compound in the individual active compound units is surrounded by a mixture of at least one sterol and at least one polymer.
7. An administration form as claimed in claim 1 and 5, wherein the acid-labile active compound is an acid-labile proton pump inhibitor.
8. An administration form as claimed in claim 1 and 5, wherein the acid-labile proton pump inhibitor is pantoprazole, omeprazole, esomeprazole, lansoprazole or rabeprazole.
9. An administration form as claimed in claim 1 and 5, wherein the acid-labile proton pump inhibitor is pantoprazole sodium sesquihydrate.

10. An administration form as claimed in claim 5, wherein the sterol is cholesterol, lanosterol, ergosterol, stigmasterol, sitosterol, brassicasterol, campesterol or mixtures thereof.
11. An administration form as claimed in claim 5, wherein the polymer is polyvidone, vinylpyrrolidone/vinyl acetate copolymer, polyvinyl acetate, methylcellulose, ethylcellulose, hydroxypropylcellulose, cellulose ester or mixtures thereof.
12. An administration form as claimed in claim 5, wherein the fatty alcohol is cetyl alcohol, myristyl alcohol, stearyl alcohol or mixtures thereof.
13. Use of an active compound unit comprising an acid-labile active compound, wherein the acid-labile active compound is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol for the manufacture of an oral administration form.
14. Process for the production of an oral administration form according to claim 1 and 5, characterized in that preparations comprising an acid-labile active compound, wherein the acid-labile active compound is surrounded by a mixture of at least one sterol and at least one polymer, by at least one fatty alcohol or by a mixture of at least one fatty alcohol and at least one polymer and/or at least one sterol are mixed with suitable pharmaceutical auxiliaries.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 98/08036

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/44 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 709 087 A (FLAMEL TECHNOLOGIES) 1 May 1996 see claims 1,6,12 ---	1-4
P,X	WO 98 52564 A (CIPLA LIMITED) 26 November 1998 see claims 1,4,9,10,16 -----	5,7-9, 11-14



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

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WO 9852564 A	26-11-1998	AU 7539098 A	11-12-1998



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(54) Title: ORAL PHARMACEUTICAL EXTENDED RELEASE DOSAGE FORM		
(57) Abstract		
<p>An enteric coated pharmaceutical extended release dosage form of an H⁺,K⁺-ATPase inhibitor giving an extended plasma concentration profile of an H⁺,K⁺-ATPase inhibitor. The extended plasma profile is obtained by a pharmaceutical composition which comprises a core material of a hydrophilic or hydrophobic matrix, and the H⁺,K⁺-ATPase inhibitor and optionally pharmaceutically acceptable excipients. The dosage form may be administered once daily.</p>		

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ORAL PHARMACEUTICAL EXTENDED RELEASE DOSAGE FORM

Field of the invention

5 The present invention is related to new pharmaceutical dosage forms which comprise a proton pump inhibitor, i.e. a H^+, K^+ -ATPase inhibitor. The new dosage forms are enteric coated formulations which provide an extended and continuous release of the H^+, K^+ -ATPase inhibitor in the small and/or large intestines resulting in an extended blood plasma profile. The formulations comprise a hydrophilic or hydrophobic matrix resulting in an
10 extended release of the H^+, K^+ -ATPase inhibitor preferably for a minimum of 2 and a maximum of 12 hours. Furthermore, the present invention refers to the manufacture of such extended release pharmaceutical formulations, and their use in medicine.

Background of the invention and prior art

15 **Acid labile H^+, K^+ -ATPase inhibitors** also named as gastric proton pump inhibitors are for instance compounds known under the generic names omeprazole, lansoprazole, pantoprazole, rabeprazole and leminoprazole. Some of these compounds are disclosed in EP-A1-0005129, EP-A1-124495, WO 94/27988, EP-A1-174726, EP-A1-166287 and GB
20 2163747.

These pharmaceutical substances are useful for inhibiting gastric acid secretion in mammals including man by controlling gastric acid secretion at the final step of the acid secretory pathway and thus reduce basal and stimulated gastric acid secretion irrespective
25 of stimulus. In a more general sense, they may be used for prevention and treatment of gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcer, duodenal ulcer and Zollinger-Ellison syndrom. Furthermore, they may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with
30 Non Ulcer Dyspepsia, and in patients with symptomatic gastro-oesophageal reflux disease

(GORD). They may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, they may be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections and diseases related to these.

Therapeutic control of gastric acid secretion is fundamental in all these diseases, but the degree and duration of acid inhibition required for optimal clinical effect is not fully understood.

It has been proposed by the Applicant in WO97/48380 (published 24 December, 1997, i.e. after the priority date of the present application) that an administration regimen that gives blood plasma levels extending from 2 to 12 hours (by any of several means) will result in a larger fraction of the proton pumps being inhibited. Thus, an extended blood plasma level should result in more effective inhibition of acid secretion resulting in improved efficacy in GORD, more rapid healing of gastric ulcer and improved eradication of *H. Pylori*. The present invention provides pharmaceutical dosage forms which achieve such extended plasma levels by an extended release of the drug.

A pharmaceutical dosage form comprising omeprazole or any other proton pump inhibitor is best protected from contact with acidic gastric juice by an enteric coating layer. In US 4,786,505 and US 4,853,230 such enteric coated preparations are described. These preparations have a core comprising an alkaline salt of the drug or a core comprising the drug together with an alkaline reacting compound, the core is coated with a water soluble or in water rapidly disintegrating separating layer and then with an enteric coating layer. WO 96/01623 and WO 96/01624 describe tableted dosage forms of omeprazole and other proton pump inhibitors, wherein enteric coating layered pellets are compressed into a multiple unit tableted dosage form. It is essential in these tableted formulations that the enteric coating layer can withstand the compression forces. None of these by the Applicant

previously described formulations gave an extended release of the drug which resulted in an extended blood plasma profile.

WO 97/02020 describes a dosage form for pantoprazol together with an antibiotic substance, which dosage form has a release-slowing membrane positioned as a intermediate layer. Said membrane comprises a water-insoluble film-forming agent as an important feature of the dosage forms. WO 97/02021 describes the same type of dosage form for a reversible proton pump inhibitor in combination with an antibiotic substance.

A facilitated way to produce extended release dosage forms compared to applying a semipermeable membrane, is to make a dosage form comprising a matrix unit. Some advantages of such matrices are for instance easier processing methods mainly by the use of common granulating and tableting equipment, and sometimes also with regard to solvents handling, energy and production time gain etc.

The use of hydrophilic matrix tablets as a principle for extended drug release was first described in the early 60's, see for instance US Patent 3,065,143. Also the hydrophobic matrix tablet principle for extended release originates from the 60's, for instance quinidine dures were on the market in 1963.

Extended release dosage forms comprising different drugs in a matrix have been described in prior art. However, none of these matrix dosage forms as such is suitable for a H^+, K^+ -ATPase inhibitor.

Some extended release hydrophilic matrix dosage forms are described in the literature for instance: In Journal of Pharmaceutical Sciences vol. 84, No. 3, March 1995, in which Kim describes dosage forms comprising theophylline or diltiazem hydrochloride. US Patent 5,273,758 describes dosage forms comprising for instance clemastine fumarate. EP 0249587 discusses felodipine formulations. Dosage forms comprising a benzodiazepine derivative are described by Franz et al in Journal of Controlled Release 1987, 5, 159-72.

Dosage forms comprising an extended release hydrophobic matrix have been described for instance by Romero et al in International Journal of Pharmacy 1991, 73, 239-48.

5 Extended release tablets with an additional coating layer have also been described, for instance by Sangalli et al in International Journal of Pharmaceutics, 91(1993), 151-6. The drugs exemplified are metoprolol tartrate and benfluorex. The described dosage form has an impermeable coating which is perforated to achieve a hole in the middle of the tablet, exposing a starting surface area for the dissolution of the inner core, i.e. dissolution of the
10 active drug.

A rather complicated dosage form was described in US Patent 5,178,867. The dosage forms had a core comprising a drug which core was coated with a semipermeable wall (maintaining its physical integrity during the life-time of the dosage form) having at least
15 one hole drilled through it as an exit port for the dissolved drug. It is also mentioned that an enteric coating layer may be applied for restricting drug delivery in the stomach and for providing drug release in the small intestine. This dosage form is much more complicated to manufacture than a matrix unit. There is no detailed description of a prepared dosage form comprising a proton pump inhibitor compound and testing of such a dosage form to
20 assure that no acidic gastric fluid is penetrating the semipermeable membrane, and that the active substance is delivered intact to the site of absorption.

None of these dosage forms provides an easy-to-produce matrix dosage form which protect an acidic susceptible substance such as a proton pump inhibitor against degradation which
25 occurs in contact with an acidic milieu such as the one found in the stomach.

Summary of the invention

Thus, the present invention relates to an enteric coated formulation with extended release properties comprising a hydrophilic or hydrophobic matrix, in which a H^+, K^+ -ATPase

inhibitor or one single enantiomer thereof, or an alkaline salt of the H^+,K^+ -ATPase inhibitor or one of its single enantiomers is incorporated.

The present invention provides a solution to the problem of making in a simplified manner such extended release dosage forms comprising an acidic susceptible H^+,K^+ -ATPase inhibitor, such as omeprazole or another proton pump inhibitor. A specific problem is that the pharmaceutical dosage forms according to the present invention must fulfill certain requirement with respect to gastric acid resistance for enteric coated articles specified in the US Pharmacopeia (Edition 23). Such as the dosage form has to be protected by an enteric coating to ensure safe delivery of the intact drug to the proper site in the gastrointestinal channel where it may be absorbed.

According to the present invention the extended plasma profile is provided by once daily administration of an enteric coated dosage form which releases the proton pump inhibitor during an extended time period, preferable during a minimum period of 2 hours and a maximum period of 12 hours. Thus, the complete dose shall have been delivered within 2 hours or at a maximum within 12 hours. The therapeutic effect of omeprazole and similar substances may be improved by providing an extended plasma profile and by providing such a dosage form for a once daily administration.

The present extended release formulations show an improved patient compliance over an administration regimen comprising consecutive administration of two or more unit doses during one day.

Detailed description of the invention.

The dosage forms giving extended release according to the present invention, are units in the form of enteric coated tablets. Alternatively, the units are enteric coated pellets, which pellets are filled into a capsule or together with tablet excipients compressed into a multiple unit tableted dosage form.

The individual units, i.e. tablets or pellets, may be constructed as a

- a core material, optionally layered on a seed/sphere, the core material comprises a hydrophilic or hydrophobic matrix containing the active drug and optionally pharmaceutically acceptable excipients, and
- 5 - an optional surrounding separating layer, and finally
- an enteric coating layer.

Core material.

- 10 The core material for the units, i.e. the tablets or the individual pellets can be constituted according to different principles. The core material may be homogenous or heterogeneous.

1) Homogenous core material.

- 15 If the core material is homogenous, it has a homogenous distribution of active substance throughout the core material.

The active substance is mixed with substances forming a hydrophilic or hydrophobic matrix and optionally pharmaceutically acceptable excipients. The core material should be
20 free from acidic substance. Thus, the hydrophilic or hydrophobic matrix in combination with other material in the core must not create an acidic reaction in the core material, which would be deleterious to the acid susceptible proton pump inhibitor compound. The micro environment around the proton pump inhibitor compound should preferably have a pH of not less than pH=7, more preferably not less than pH=8, when water is absorbed to the
25 particles of the mixture or when water is added in small amount to the mixture.

The active substance may be mixed with further components to obtain preferred handling and processing properties and a suitable concentration of the active substance in the final mixture. Such components can be binders, surfactants, lubricants, glidants, fillers, alkaline
30 additives or other pharmaceutically acceptable ingredients, alone or in mixtures.

Said core material may be produced either by direct compression of the mixed ingredients, or by granulation of the ingredients followed by compression of the dried granulated material.

5

In direct compression, the ingredients are mixed and compressed by using ordinary tableting equipment.

10

For the granulation there are numerous alternatives of granulating procedures mentioned in the literature, dry methods like roller compaction (Chilsonator) and wet methods utilizing granulating solutions with and without the addition of binders. A variant of the wet methods is to make a spray-granulation in a fluid bed.

15

For the wet granulating methods either organic solvents, aqueous solutions or pure water may be utilized to prepare the granulating solutions. Due to environmental considerations pure water is preferred. However, for some of the materials used as hydrophilic matrix components, the technical properties of the produced granules might be better when using organic solvents such as alcohols, this is especially noticeable for hydroxypropyl methylcelluloses.

20

For granulation of the hydrophobic matrix components it is also preferred to use alcoholic solvents in wet granulation methods. As binders in these solution, one or more of the polymers listed below, as matrix forming polymers may be chosen.

25

As a general principle the active ingredients together with matrix forming polymers and optionally pharmaceutically acceptable excipients are mixed and granulated. Dried granules are optionally mixed with pharmaceutically acceptable excipients, and then compressed to tablets utilizing common equipment.

The size of the formulated core materials is approximately between 2 and 14 mm, preferably between 3 and 9 mm for a tablet preparation, and between 0.1 and 4 mm, preferably between 0.1 and 2 mm for a pellet preparation.

5 *II) Heterogenous core material.*

Alternatively, the core material may be heterogeneous with an inner zone, for instance a seed or sphere, not containing the active substance. This seed or sphere is surrounded by a layer of a hydrophilic or hydrophobic matrix containing the active substance, and
10 optionally pharmaceutically acceptable excipients are incorporated in the matrix.

The seed or sphere may be soluble or insoluble. Optionally, the seed or sphere (inner zone) may be coated with an inert layer to prepare a smooth surface before the layer containing active substance and hydrophilic or hydrophobic eroding substance(s) is applied onto the
15 seed/sphere.

Insoluble seeds/spheres may comprise different oxides, celluloses, organic polymers and other materials, alone or in mixtures. Water soluble seeds/spheres may comprise different inorganic salts, sugars and other materials, alone or in mixtures. The size of the seeds may
20 vary between approximately 0.1 and 2 mm. The seeds layered with the matrix containing the active substance are produced either by powder or solution/suspension layering using for instance granulating or spray coating/layering equipment.

Pharmaceutically acceptable additives.

25

Binders for a hydrophilic matrix can be chosen among the hydrophilic eroding matrices mentioned below, and in addition from sugars, polyvinyl pyrrolidine, starches and gelatine.

Binders for a hydrophobic matrix can be chosen among the hydrophobic eroding matrices
30 mentioned below.

Additives listed among the following components are suitable both for a hydrophilic as well as a hydrophobic matrix.

Suitable alkaline additives can be chosen among, but are not restricted to, substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$,

$\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids such as arginine, and their salts or other similar pharmaceutically acceptable pH-buffering substances.

Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic surfactants, such as polysorbate 80, or ionic surfactants such as for instance sodium lauryl sulfate.

Lubricants are for instance magnesium stearate, sodium stearyl fumarate (PruvTM), and cetyl palmitate.

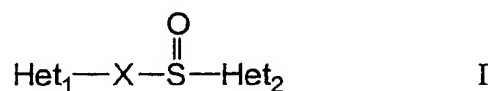
Fillers are for instance sodium aluminium silicate, lactose, calcium phosphate, and others.

Glidants are for instance talc and aerosil.

Antioxidants may be added when appropriate.

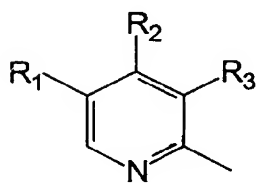
Active substance.

Compounds of interest for the novel extended release dosage forms according to the present invention are compounds of the general formula I, an alkaline salt thereof, one of the single enantiomers thereof or an alkaline salt of one of the enantiomers

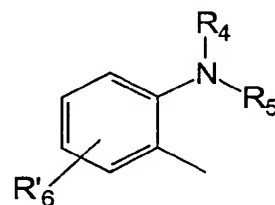


wherein

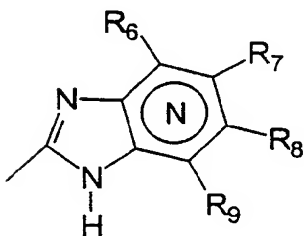
Het₁ is



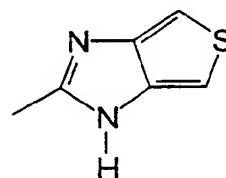
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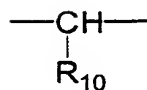
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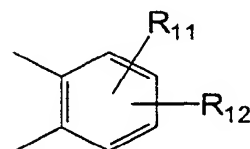
or



X =



or



wherein

N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

5 R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino, morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and arylalkyl;

10

R₆' is hydrogen, halogen, trifluoromethyl, alkyl or alkoxy;

R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxy carbonyl, oxazoliny, trifluoroalkyl, or adjacent groups R₆-R₉

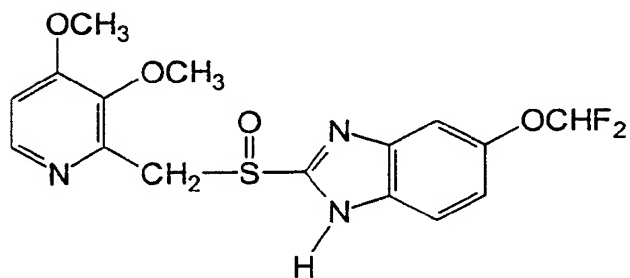
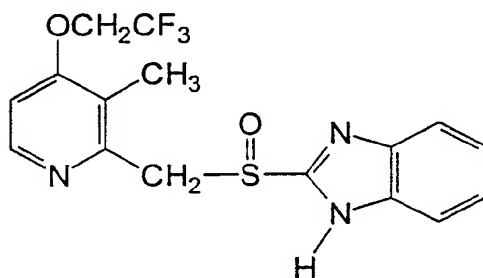
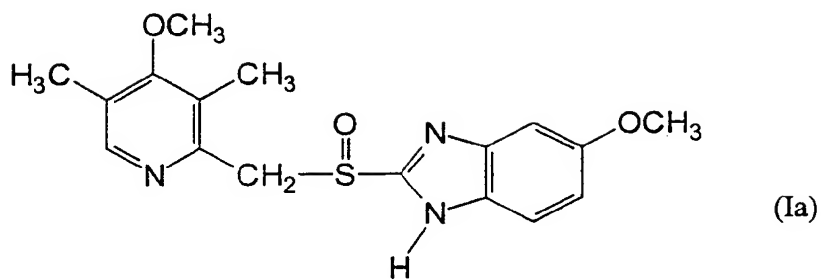
15 form ring structures which may be further substituted;

R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

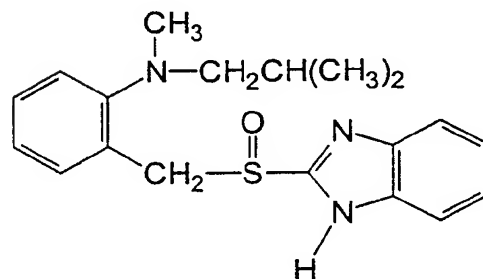
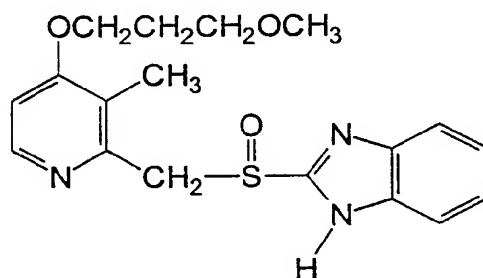
R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl.

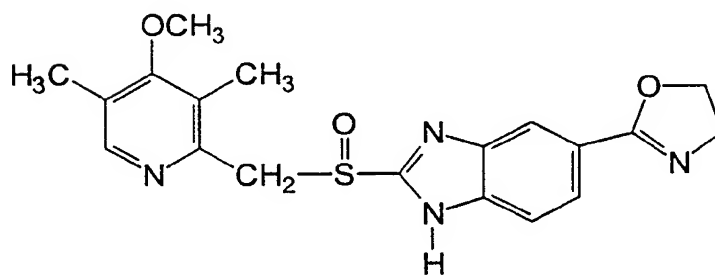
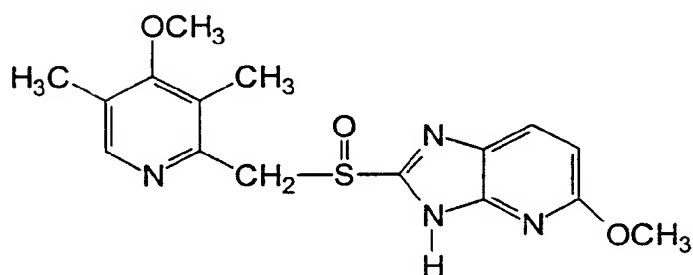
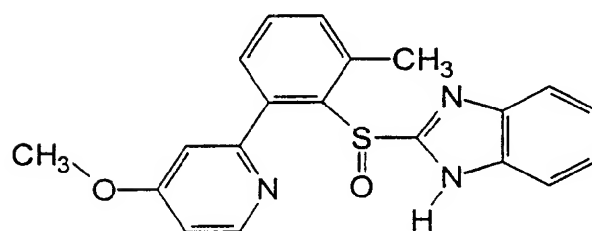
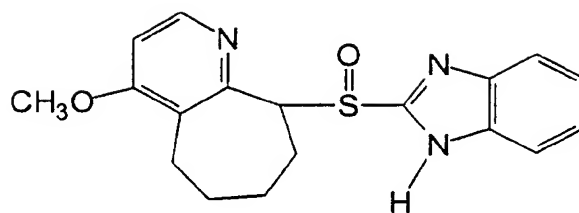
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Examples of specifically interesting compounds according to formula I are



5





- 10 The compound suitable to be used the extended release formulations according to the present invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+} , Ca^{2+} , Na^{+} or K^{+} salts, preferably the Mg^{2+} salts. The compounds may

also be used in the form of one of its single enantiomers or an alkaline salt of the single enantiomer.

Preferred compounds for the oral pharmaceutical preparations according to the present invention are omeprazole, a magnesium salt of omeprazole or a magnesium salt of the (-)-enantiomer of omeprazole. Omeprazole and related substances as well as their preparations are described in EP 5129, EP 124 495, WO 95/01977, WO 94/27988 hereby incorporated in a whole by references.

The above compounds are susceptible to degradation/transformation in acidic and neutral media. Generally, the degradation is catalyzed by acidic reacting compounds and the active compounds are stabilized with alkaline reacting compounds. There are different enteric coating layered preparations comprising omeprazole as well as other proton pump inhibitors described in the prior art, see for instance US-A 4,853,230, WO 95/ 01783 and WO 96/ 01623. Especially, the latter describes alternative manufacturing methods for the preparation of enteric coating layered pellets comprising omeprazole and similar compounds. These patents are hereby incorporated in whole by references.

Hydrophilic matrix.

The active substance, i.e. the drug, is embedded in a hydrophilic polymer optionally together with pharmaceutically acceptable excipients. Suitable hydrophilic polymers are for instance hydroxypropyl methylcellulose, hydroxypropyl cellulose, ethylhydroxyethylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, polyethylene oxides, polyvinyl alcohols, tragacanth, and xanthan. These polymers can be used alone or in mixtures with each other.

The amount of hydrophilic polymer in the matrix is preferably 15-80 % (calculated on the unit weight), and the hydrophilic polymer(s) chosen among the above mentioned.

Especially preferred polymers in the hydrophilic matrix unit are hydroxypropyl methylcellulose or polyethylene oxides.

Excipients preferred in the matrix are fillers which result in good technical tableting properties, i.e. sodium aluminium silicate, mannitol or calcium phosphate (EmcompressTM). A preferred matrix comprises 15-80% w/w (calculated on the unit weight) of a hydrophilic polymer chosen as above, and 10-60% w/w (calculated on the unit weight) of sodium aluminium silicate or calciumphosphate (EmcompressTM).

Hydrophobic matrix.

The active substance, i.e. the drug, is embedded in a hydrophobic matrix optionally together with pharmaceutically acceptable excipients. The hydrophobic matrix comprises a hydrophobizing agent and/or a hydrophobic polymer. Suitable material for the hydrophobic matrix are for instance a hydrophobizing agents such as cetanol, cetostearyl alcohol, cetyl palmitate, waxes like carnauba wax, paraffin, magnesium stearate, sodium stearyl fumarate, and medium- or long- chain glycerol esters alone or in any mixtures.

Hydrophobic polymers are exemplified by for instance polyvinyl chloride, ethyl cellulose, polyvinyl acetate and acrylic acid copolymers, such as EudragithTM RS and RL. The polymers can be used alone or as mixtures.

As binders for the hydrophobic matrix may be used either hydrophilic or hydrophobic polymers.

It is important that the matrix comprises at least one component that is soluble in media such as the intestinal fluids. This component dissolves and leaves a porous network open for passage of dissolving fluids and dissolved drug. This soluble component may be the active drug itself, or a soluble component such as a sugar. Preferably the soluble component is present in an amount of not less than 2% w/w (calculated on the unit weight) and up to 60%.

It is preferred that the matrix comprises not less than 10 % w/w (calculated on the unit weight) and up to 80% of a hydrophobizing agent or a hydrophobic polymer, both described above, or any combinations thereof.

5 Another preferred matrix comprises as an additive a slightly soluble or less soluble component. As such components may any of the following be added: sodium aluminium silicate, calciumphosphate, aerosil, titaniumdioxide, magnesium carbonates, or other neutral or alkaline compounds that are slightly soluble or less soluble, herein with regard to solubility in water. Slightly soluble is defined in compliance with the European
10 Pharmacopiea (Edition 3) under the heading "General notices". Such a matrix comprises 10-80 % w/w (calculated on the unit weight) of a hydrophobizing agent or a hydrophobic polymer or any combinations thereof, together with 10% - 60% of a slightly soluble or less soluble component. As such a component is especially preferred sodium aluminium silicate.

15

The final dissolution profile may sometimes be adjusted by thermal treatment of the hydrophobic matrix unit for a short period, to achieve temperatures at or above the softening temperature of the hydrophobizing agents. Such a treatment is most suitably performed after the enteric coating has been completed.

20

Enteric coating layer(s) and separating layer(s).

25

Before applying an enteric coating layer onto the core material, the pellet or tablet may optionally be covered with one or more separating layers comprising pharmaceutical
excipients optionally including alkaline compounds such as for instance pH-buffering
compounds. This separating layer separates the active substance in the pellets or tablets
from the outer enteric coating layer.

30

The separating layer can be applied to by coating or layering procedures in suitable equipments such as coating pan, coating granulator, centrifugal granulator in a fluidized

bed apparatus (including Wuster type) using water and/or organic solvents for the coating process. As an alternative the layer(s) can be applied by using powder coating or press-coating techniques.

- 5 Suitable materials for the separating layer are pharmaceutically acceptable compounds such as, for instance, sugar, polyethylene glycol, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static
10 agents, such as for instance magnesium stearate, titanium dioxide, talc, pH-buffering substances and other additives may also be included into the separating layer.

When the optional separating layer is applied to the pellets or tablets it may constitute a variable thickness. The maximum thickness of the optional separating layer is normally
15 only limited by processing conditions. The separating layer may serve as a diffusion barrier and may act as a pH-buffering zone. The optionally separating layer may improve the chemical stability of the active substance and/or the physical properties of the dosage form.

- 20 Finally the units, i.e. the tablets or pellets, are covered by one or more enteric coating layers by using a suitable coating technique. The enteric coating layer material may be dispersed or dissolved in either water or in suitable organic solvents. As enteric coating layer polymers one or more, separately or in combination, of the following can be used; e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate,
25 hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethylcellulose, shellac or other suitable enteric coating layer polymer(s).

- Additives such as dispersants, colorants, pigments, additional polymers e.g.
30 poly(ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer. Other compounds may be added to increase film

thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material. The enteric coating layer(s) constitutes a thickness of approximately at least 10 μm , preferably more than 20 μm . The maximum thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

5

The enteric coating layers may also contain pharmaceutically acceptable plasticizers to obtain desired mechanical properties. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, glucerol monoesters, polysorbates or other plasticizers and mixtures thereof. The amount of plasticizer is preferably optimized for each formula, in relation to the selected polymer(s), selected plasticizer(s) and the applied amount of said polymer(s).

10

Final dosage form

15

The enteric coated tablet, or pellet optionally mixed with tablet excipients are filled into a capsule, or compressed into a multiple unit tableted dosage form. Prepared enteric coated tablets are optionally covered with filmforming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a tablet coating layer may further comprise additives like anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

20

The dosage forms according to the invention are suitable for oral administration. The dose will depend on the nature and severity of the disease to be treated. The dose may also vary according to the age, body weight, and response of the individual patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. In the treatment of other conditions higher doses than average will be used. The dosage form may also be used in combinations with other dosage forms comprising for instance NSAID(s), motility agents, antibacterial substances, and/or antacids.

25

30

A unit dosage of the proton pump inhibitor is administered at least once a day. The oral pharmaceutical formulation will maintain an extended release of the pharmaceutical substance of a minimum of 2 and a maximum of 12 hours, preferably is maintained for a minimum of 4 and a maximum of 8 hours. Such an extended release preparation may
5 comprise up to 500 mg of the substance, preferably the doses comprise about 5 - 100 mg of the substance, and more preferably 10 - 80 mg.

Examples

10 The invention is described more in detail by the following non-limiting examples.

Example 1.

Extended release matrix tablets comprising Omeprazole -Mg (approx. 20 mg).

15 Granules for tablet cores were made according to the following composition (parts by weight);

Omeprazole-Mg	45
Polyethylene oxide (mwt approx. 4000 000), Polyox® WSR 301	195
ethanol 95% (w/v)	97

The powders were mixed in a mixer after which the ethanol was added in an even stream.

20 The mass was dried in a drying oven at 50°C.

After milling in an oscillating mill through a 1.0 mm screen the obtained granules were mixed with tablet lubricant, according to the following composition (parts by weight) ;

Granules for tablet core	235
Sodium stearyl fumarate (Pruv®)	1

The mixing was performed in a Kenwood mixer, and the mixture was compressed to tablets (6 mm in diameter) having an average weight of 123 mg, on a single punch tableting machine (Diaf).

The dissolution rate was tested by analyzing individual tablets using USP dissolution apparatus No. 2 (paddle) equipped with a stationary basket and operated at 100 rpm and 37°C. The dissolution medium was phosphate buffer pH 6.8.

The release rate obtained (n=2) is shown in table below;

Time (Hours)	Released (% of dose)
0.5	4-4
1	7-8
3	20-21
5	31-33
10	59-67
15	84-86
20	95-96

10

The prepared tablets can be further processed according to Example 3 or 4, i.e. apply an enteric coating on the tablet.

Example 2.

15 Extended release matrix tablets comprising S-omeprazole Mg-salt (approx. 32 mg).

Granules for tablet cores were made according to the following composition (parts by weight);

S-omeprazole Mg-salt

300

Hydroxypropyl methylcellulose 50 cps	80
ethanol 95% (w/v)	356
Polyvinyl pyrrolidone K-90	40

The powders were mixed in a mixer after which the ethanol was added in an even stream.
The mass was dried in a drying oven at 50°C.

- 5 After milling in an oscillating mill through a 1.0 mm screen the obtained granules were mixed with tablet lubricant, according to the following composition (parts by weight);

Granules for tablet core	380
Sodium stearyl fumarate (Pruv®)	4

- 10 The mixing was performed in a Kenwood mixer whereafter the mixture was compressed to tablets (7 mm in diameter) having an average weight of 175 mg, on a single punch tableting machine (Diaf).

The prepared tablets can be further processed according to Example 3 or 4, i.e. apply an enteric coating on the tablet.

15

Example 3.

Enteric coated extended release matrix tablets comprising S-omeprazole Mg-salt (approx. 32 mg).

- 20 Tablets from example 2 were coated first with a separating layer in a fluidized bed coating apparatus with a coating suspension of the following composition;

EtOH 99.5% (w/v)	85 parts by weight
Water purified	85 parts by weight
Hydroxypropyl methylcellulose 6 cps	10 parts by weight

Talc, micronized 2 parts by weight

Sum: 182 parts.

200 grams of tablets were processed and the coating was continued until average tablet weight was 181 mg.

- 5 The tablets coated with a separating layer were coated with an enteric coating layer in the same equipment as for the preceding coating step. The coating solution used had the following composition;

Hydroxypropyl methylcellulose phtalate (HP-55®) 19 parts by weight

Cetanol 1 parts by weight

Acetone 182 parts by weight

Ethanol (95% w/v) 78 parts by weight

Sum: 280 parts

- 10 100 grams of the separating layer coated tablets were processed and the coating was continued until average tablet weight was 194 mg.

The tablets were exposed for 0.1 M HCl for 2 hours. The acid resistance was determined to 98%.

15

Example 4.

Enteric coated extended release matrix tablets comprising S-omeprazole Mg-salt (approx. 32 mg).

- 20 The tablets obtained from Example 2 were directly coated with an enteric coating layer in a fluidized bed coating apparatus. The coating solution used had the following composition;

Hydroxypropyl methylcellulose phtalate (HP-55®)	19	parts by weight
Cetanol	1	parts by weight
Acetone	182	parts by weight
Ethanol (95% w/v)	78	parts by weight
Sum:	280	parts

100 grams of the tablets were processed and the coating was continued until average tablet weight was 187 mg.

- 5 The tablets were exposed for 0.1 M HCl for 2 hours. The acid resistance was determined to 99%.

Example 5.

Extended release matrix tablets comprising S-omeprazole Mg-salt (approx. 45 mg).

10

Granules for tablet cores were made according to the following composition (parts by weight);

S-omeprazole Mg-salt	45
Polyethylene oxide (mwt approx. 4000 000), Polyox® WSR 301	145
Sodium aluminium silicate	50
Propyl gallate	0.1
Ethanol 99.5% (w/v)	140

- 15 The powders were mixed and moistened with the ethanol in a mixer after which the mass was dried in a drying oven at 50°C.

After milling in an oscillating mill through a 1.0 mm screen the obtained granules were mixed with tablet lubricant, according to the following composition (parts by weight);

20

Granules for tablet core 232

Sodium stearyl fumarate (Pruv®) 1

The ingredients were mixed whereafter the mixture was compressed to tablets (10 mm in diameter) having an average weight of 241 mg, on a single punch tableting machine (Diaf).

5 Dissolution rate was tested as described in example 1.

The release rate obtained (n=2) is shown in table below;

Time (Hours)	Released (% of dose)
2	16-16
4	29-29
6	41-42
8	53-54
10	65-66
12	76-78
14	88-88
16	95-96
18	100-100
20	109-109 *)

*) Remark: the complete dose has been released.

10

Example 6.

Extended release matrix tablets comprising S-omeprazole Mg-salt (approx. 45 mg).

Granules for tablet cores were made according to the following composition (parts by weight);

15

S-omeprazole Mg-salt	45
Polyethylene oxide (mwt approx. 4000 000), Polyox® WSR 301	72.5
Polyethylene oxide (mwt approx. 100 000), Polyox® WSR N10	72.5
Sodium aluminium silicate	50
Propyl gallate	0.1
Ethanol 99.5% (w/v)	140

The powders were mixed and moistened with the ethanol in a mixer after which the mass was dried in a drying oven at 50°C.

5

After milling in an oscillating mill through a 1.0 mm screen the obtained granules were mixed with tablet lubricant, according to the following composition (parts by weight);

Granules for tablet core	234
Sodium stearyl fumarate (Pruv®)	1

10 The ingredients were mixed whereafter the mixture was compressed to tablets (10 mm in diameter) having an average weight of 241 mg, on a single punch tableting machine (Diaf).

Dissolution rate was tested as described in Example 1 above.

15 The release rate obtained (n=2) is shown in table below;

Time (Hours)	Released (% of dose)
2	14-14
4	29-29
6	44-47
8	60-65
10	73-78
12	87-89
14	99-101
16	101-102 *)
18	101-105 *)

*) Remark: The complete dose has been released

Example 7.

- s Extended release matrix tablets comprising S-omeprazole Mg-salt (approx. 45 mg).

Granules for tablet cores were made according to the following composition (parts by weight);

S-omeprazole Mg-salt	45
Polyethylene oxide (mwt approx. 100 000), Polyox® WSR N10	145
Sodium aluminium silicate	50
Propyl gallate	0.1
Ethanol 99.5% (w/v)	140

10

The powders were mixed and moistened with the ethanol in a mixer after which the mass was dried in a drying oven at 50°C.

After milling in an oscillating mill through a 1.0 mm screen the obtained granules were mixed with tablet lubricant, according to the following recipe (parts by weight);

Granules for tablet core	229
Sodium stearyl fumarate (Pruv®)	1

- 5 The ingredients were mixed whereafter the mixture was compressed to tablets (10 mm in diameter) having an average weight of 241 mg, on a single punch tableting machine (Diaf).

Dissolution rate was tested as described in example 1.

The release rate obtained (n=2) is shown in table below;

10

Time (Hours)	Released (% of dose)
2	67-68
4	107-110 *)
6	107-111 *)

*) Remark: The complete dose has been released.

Example 8.

- 15 Extended release matrix tablets comprising omeprazole Mg-salt (approx. 45 mg).

Granules for tablet cores were made according to the following composition (parts by weight);

Omeprazole Mg-salt	80
Hydroxypropyl methylcellulose 50 cps	300
Polyvinyl pyrrolidone K-90	40
Ethanol 99.5% (w/v)	400

The polyvinyl pyrrolidone (PVP) was dissolved in the alcohol. The other two ingredients were mixed and then moistened with the PVP-solution in a mixer. Thereafter the obtained mass was dried in a drying oven at 50°C.

5

After milling in an oscillating mill through a 1.0 mm screen the obtained granules were mixed with tablet lubricant, according to the following composition (parts by weight);

Granules for tablet core	412
Sodium stearyl fumarate (Pruv®)	4

10 The ingredients were mixed whereafter the mixture was compressed to tablets (9 mm in diameter) having an average weight of 265 mg, on a single punch tableting machine (Diaf).

Example 9.

Extended release matrix tablets comprising S-omeprazole Mg-salt (approx. 45 mg).

15

Granules for tablet cores were made according to the following composition (parts by weight);

S-omeprazole Mg-salt	74
Hydroxypropyl methylcellulose 50 cps	210
Hydroxypropyl methylcellulose 10000 cps	90
Polyvinyl pyrrolidone K-90	40
Ethanol 99.5% (w/v)	400

The polyvinyl pyrrolidone (PVP) was dissolved in the alcohol. The other ingredients were mixed and then moistened with the PVP-solution in a mixer. Thereafter the obtained mass was dried in a drying oven at 50°C.

- 5 After milling in an oscillating mill through a 1.0 mm screen the obtained granules were mixed with tablet lubricant, according to the following composition (parts by weight);

Granules for tablet core	378
Sodium stearyl fumarate (Pruv®)	4

- 10 The mixing was performed in a mixer, and the mixture was compressed to tablets (9 mm in diameter) having an average weight of 261 mg, on a single punch tableting machine (Diaf).

Dissolution rate was tested in phosphate buffer pH 6.8 as described in example 1.

The release rate obtained (n=6) is shown in table below;

Time (Hours)	Average (min-max) Released (% of nominal dose)
1	8 (8-8)
2	16 (16-17)
3	26 (25-27)
4	35 (34-36)
6	54 (52-56)
8	72 (70-75)
10	86 (83-91)
12	92 (90-99)

Example 10.

Extended release matrix tablets comprising S-omeprazole Mg-salt (approx. 55 mg).

Granules for tablet cores were made according to the following composition (parts by weight);

S-omeprazole Mg-salt	40
Polyvinyl alcohol mwt 22000, degree of hydrolysis 97.5-99.5%	160
Polyvinyl pyrrolidone K-90	14
Ethanol 99.5% (w/v)	49

The polyvinyl pyrrolidone (PVP) was dissolved in the alcohol. The other two ingredients were mixed and then moistened with the PVP-solution in a mixer. Thereafter the obtained mass was dried in a drying oven at 50°C.

After milling in an oscillating mill through a 1.0 mm screen the obtained granules were mixed with tablet lubricant, according to the following composition (parts by weight);

Granules for tablet core	215
Sodium stearyl fumarate (Pruv®)	2

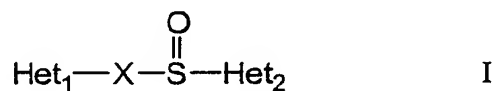
The ingredients were mixed whereafter the mixture was compressed to tablets (9 mm in diameter) having an average weight of 310 mg, on a single punch tableting machine (Diaf).

Dissolution rate was tested in phosphate buffer pH 6.8 as described in example 1. The release rate obtained (n=2) is shown in table below;

Time (Hours)	Released Average (min-max) % (of in tablets found <u>dose</u>)
1	5 (5-5)
2	15 (15-15)
4	24 (23-24)
6	31 (30-32)
8	38 (37-39)
10	44 (43-45)
12	50 (49-50)
14	55 (55-56)

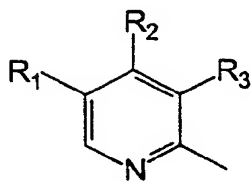
Claims

1. An enteric coated pharmaceutical extended release dosage form of a H^+ , K^+ -ATPase inhibitor, characterized in that the dosage form comprises a core material of a hydrophilic matrix or a hydrophobic matrix and the H^+ , K^+ -ATPase inhibitor, and that the H^+ , K^+ -ATPase inhibitor is a compound of formula I, an alkaline salt thereof, one of the single enantiomers thereof or an alkaline salt of one of the enantiomers of a compound of formula I

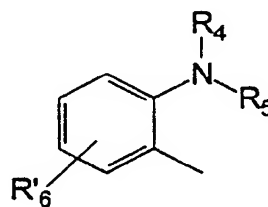


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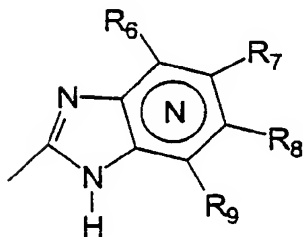
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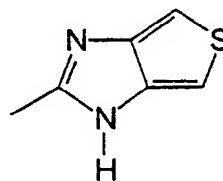
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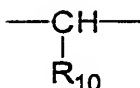
Het_2 is



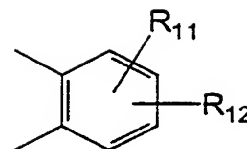
or



X =



or



wherein

- 5 N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino,
10 morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and arylalkyl;

R₆' is hydrogen, halogen, trifluoromethyl, alkyl or alkoxy;

- 15 R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxy carbonyl, oxazoliny, trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

20

R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl.

2. A dosage form according to claim 1 characterized in that the H⁺, K⁺-ATPase inhibitor is a compound selected from the group of omeprazole, an alkaline salt of omeprazole, the (-)
25)-enantiomer of omeprazole and an alkaline salt of the (-)-enantiomer of omeprazole.

3. A dosage form according to claim 2, characterized in the alkaline salt is a magnesium salt.
- 5 4. A dosage form according to claim 1 characterized in that the H^+ , K^+ -ATPase inhibitor is a compound selected from the group of lansoprazole, pantoprazole, alkaline salts thereof, a single enantiomer thereof, and an alkaline salt thereof.
5. A dosage form according to any of claims 1-4 characterized in that the core material is
10 layered with a separating layer, which is present under the enteric coating layer.
6. A dosage form according to any of claims 1-5 characterized in that the core material further comprises pharmaceutically acceptable excipients.
- 15 7. A dosage form according to any of claims 1-6, characterized in that the core material **further comprises alkaline additives.**
8. A dosage form according to any of claims 1-7 characterized in that the core material comprises a seed layered with the H^+ , K^+ -ATPase inhibitor and the hydrophilic or
20 hydrophobic matrix, and optionally pharmaceutically acceptable excipient.
9. A dosage form according to any of claims 1-8 characterized in that the core material creates a micro-environment around the H^+ , K^+ -ATPase inhibitor of not less than pH=7.
- 25 10. A dosage form according to any of claims 1-9 characterized in that the hydrophilic matrix comprises a hydrophilic polymer selected from the group of : hydroxypropyl methylcellulose, hydroxypropyl cellulose, ethylhydroxy ethylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, polyethylene oxides, polyvinylpyrrolidone, polyvinyl alcohols, tragacanth, and xanthan, or
30 any mixtures thereof.

11. A dosage form according to claim 10 characterized in that the hydrophilic matrix further comprises a filler, such as sodium aluminium silicate.

5 12. A dosage form according to any of claims 1-9 characterized in that the hydrophobic matrix comprises a hydrophobic polymer and a hydrophobizing agent, the hydrophobizing agent is selected from the group of : cetanol, cetostearyl alcohol, cetyl palmitate, waxes like carnauba wax, paraffin, magnesium stearate, sodium stearyl fumarate, and medium- or long- chain glycerol esters alone or mixtures thereof.

10

13. A dosage form according to claim 12 characterized in that the hydrophobic polymer is selected from the group of : polyvinyl chloride, ethyl cellulose, polyvinyl acetate and acrylic acid copolymers.

15 14. A dosage form according to claims 12 or 13 characterized in that the hydrophobic matrix further comprises a slightly soluble or less soluble component selected from the group of : sodium aluminium silicate, calcium phosphate, aerosil, titanium dioxide, and magnesium carbonates.

20 15. A process for the manufacture of an enteric coated dosage form comprising a H^+ , K^+ -ATPase inhibitor and a hydrophilic matrix or a hydrophobic matrix and optionally pharmaceutically acceptable excipient, characterized in that the process comprises the follow steps:

25 a) a core material is shaped comprising the H^+ , K^+ -ATPase inhibitor and the hydrophilic matrix or the hydrophobic matrix, and optionally pharmaceutically acceptable excipient,

b) optionally a separating layer is applied onto the core material, and

30 c) an enteric coating layer is applied onto the core material from step a) or step b).

16. A dosage form according to any of claims 1 - 14 characterized in that the extended release is maintained for a minimum of 2 hours and a maximum of 12 hours.

5 17. A dosage form according to any of claims 1 - 14 for use in therapy.

18. Use of an oral pharmaceutical composition as claimed in any of claims 1 - 14 in the manufacture of a medicament with improved inhibition of gastric acid secretion.

10 19. Use of an oral pharmaceutical composition as claimed in any of claims 1 - 14 in the manufacture of a medicament with improved therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion.

20. Use of H^+ , K^+ - ATPase inhibitor with the formula I defined in claim 1, for the
15 preparation of a pharmaceutical composition with extended release.

21. A method for improving inhibition of gastric acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical composition as claimed in any of claims 1 -14.

20

22. A method for improving the therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical composition as claimed in any claims 1 -14.

25 23. A method for receiving an extended plasma profile of a H^+ , K^+ - ATPase inhibitor by administering to a patient in need thereof a pharmaceutical preparation with extended release of a H^+ , K^+ - ATPase inhibitor as defined in any of claims 1-14.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/02368

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/20, A61K 9/22, A61K 9/52, A61K 31/44, A61K 31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9747285 A1 (DEPOMED, INC.), 18 December 1997 (18.12.97), page 3, line 20 - line 22; page 3, line 32 - line 34; page 4, line 25 - line 27, page 5, line 1 - line 4; page 7, line 18 - line 20	1-3,7,14-19, 1-3,10,17-23
Y	--	4-9,11-16
Y	WO 9702020 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH), 23 January 1997 (23.01.97), page 4, line 15 - line 23; page 5, line 16 - line 18; page 6, line 11 - line 15, page 6, line 20 - line 22; page 8, line 30 - line 31; page 9, line 2 - line 13 -----	4-9,11-16

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

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Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT
Information on patent family members

02/03/99

International application No.

PCT/SE 98/02368

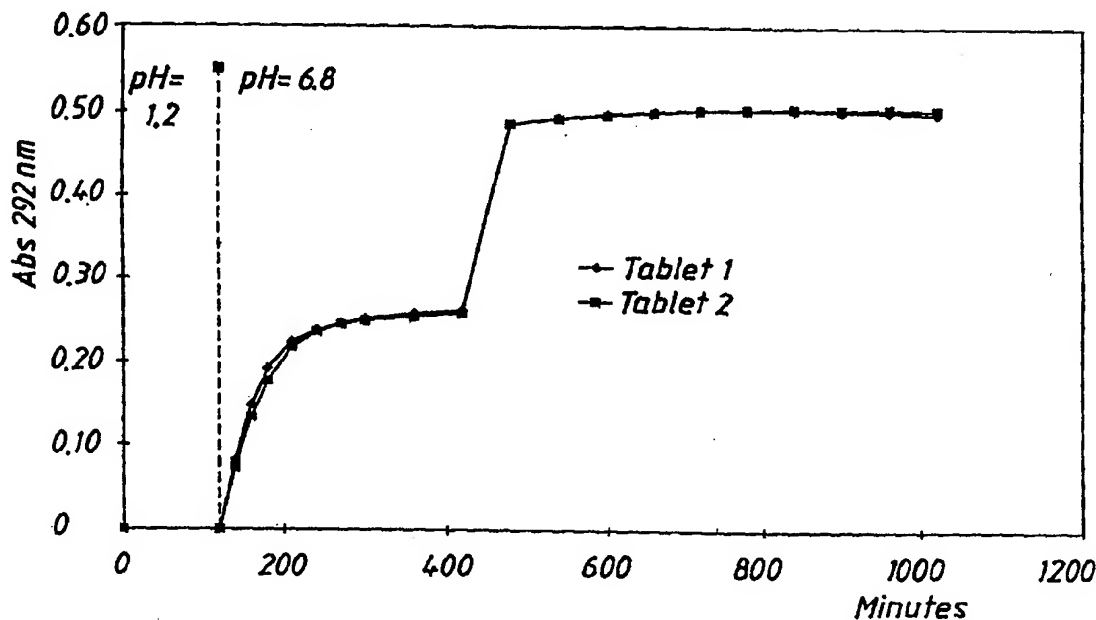
Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9747285 A1	18/12/97	AU 3290397 A	07/01/98
WO 9702020 A1	23/01/97	AU 6517496 A	05/02/97
		CA 2232450 A	23/01/97
		EP 0841903 A	20/05/98



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/26, 9/54, 31/44, 31/41	A1	(11) International Publication Number: WO 99/32093
		(43) International Publication Date: 1 July 1999 (01.07.99)
(21) International Application Number: PCT/SE98/02369		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
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(30) Priority Data: 9704870-6 22 December 1997 (22.12.97) SE		
(71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).		
(72) Inventors; and (75) Inventors/Applicants (for US only): LUNDBERG, Per, Johan [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). SJÖBLOM, Brita [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE).		
(74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).		Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>

(54) Title: ORAL PHARMACEUTICAL PULSED RELEASE DOSAGE FORM



(57) Abstract

An enteric coated pharmaceutical dosage form comprising a H^+ , K^+ -ATPase inhibitor. The dosage form comprises at least two portions of the H^+ , K^+ -ATPase inhibitor to be released in at least two consecutive pulses. The dosage form has at least one fraction with a pulsed delayed release and another fraction with instant release of the H^+ , K^+ -ATPase inhibitor. The portions are released in time by from 0.5 and up to 12 hours interval, preferably by from 0.5 and up to 8 hours, and more preferably by from 0.5 and up to 4 hours interval. The dosage form is intended for once daily administration.

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ORAL PHARMACEUTICAL PULSED RELEASE DOSAGE FORM

Field of the invention

5 The present invention is related to new oral pharmaceutical dosage forms which comprise a proton pump inhibitor, i.e. a H^+, K^+ -ATPase inhibitor. The new dosage forms are enteric coated formulations which provide a discontinuous pattern of two or more discrete release pulses of the H^+, K^+ -ATPase inhibitor in the small and/or large intestines. The pulses are separated in time by from 0.5 and up to 12 hours, they are preferably separated by from 0.5
10 and up to 6 hours, and more preferably from 0.5 and up to 4 hours. Furthermore, the present invention refers to the manufacture of such pulsed delayed release pharmaceutical formulations, and their use in medicine.

Background of the invention and prior art

15 Acid labile H^+, K^+ -ATPase inhibitors also named as gastric proton pump inhibitors are for instance compounds known under the generic names omeprazole, lansoprazole, pantoprazole, rabeprazole and leminoprazole. Some of these compounds are disclosed in EP-A1-0005129, EP-A1-124495, WO 94/27988, EP-A1-174726, EP-A1-166287 and GB
20 2163747.

These pharmaceutical substances are useful for inhibiting gastric acid secretion in mammals including man by controlling gastric acid secretion at the final step of the acid secretory pathway and thus reduce basal and stimulated gastric acid secretion irrespective
25 of stimulus. In a more general sense, they may be used for prevention and treatment of gastric-acid related diseases in mammals and man, including e.g. reflux oesophagitis, gastritis, duodenitis, gastric ulcer, duodenal ulcer and Zollinger-Ellison syndrom. Furthermore, they may be used for treatment of other gastrointestinal disorders where gastric acid inhibitory effect is desirable e.g. in patients on NSAID therapy, in patients with
30 Non Ulcer Dyspepsia, and in patients with symptomatic gastro-oesophageal reflux disease

(GORD). They may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding, pre-and post-operatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, they may be useful in the treatment of psoriasis as well as in the treatment of *Helicobacter* infections and diseases related to these.

Therapeutic control of gastric acid secretion is fundamental in all these disease, but the degree and duration of acid inhibition required for optimal clinical effect is not fully understood.

10

It has been proposed by the Applicant in WO97/48380, (published 24 December, 1997 i.e. after the priority date of the instant application,) that an administration regimen that gives blood plasma levels extending from 2-12 hours (by any of several means) will result in a larger fraction of proton pumps being inhibited. Thus, an extended blood plasma level should result in more effective inhibition of acid secretion resulting in improved efficacy in GORD, more rapid healing of gastric ulcer and improved eradication of *H. Pylori*. The present invention provides pharmaceutically dosage forms which achieve such extended plasma levels by releasing the drug in two or more separate pulses.

20 A pharmaceutical dosage form of omeprazole or any other proton pump inhibitor is best protected from contact with acidic gastric juice by an enteric coating layer. In US 4,786,505 and US 4,853,230 such enteric coated preparations are described. These preparations have a core comprising an alkaline salt of the drug or a core comprising the drug together with an alkaline reacting compound, the core is coated with a water soluble or in water rapidly disintegrating separating layer and then with an enteric coating layer.

25 WO 96/01623 and WO 96/01624 describe tableted dosage forms of omeprazole and other proton pump inhibitors, wherein enteric coating layered pellets are compressed into a multiple unit tableted dosage form. It is essential in these tableted formulations that the enteric coating layer can withstand the compression forces. None of these by the Applicant

30 previously described formulations gave a dissolution of two or more pulses separated in

time, i.e. in the meaning pulsed release of the proton pump inhibitor which resulted in an extended blood plasma profile.

There are different technologies and pharmaceutical formulations described in the prior art which aim at a delayed release of an administered drug. Such pharmaceutical formulations are for instance formulations providing different lag times, constructions based on osmotic differences, slow-eroding/dissolving layers, time controlled explosion systems or any combinations thereof. In the following some of these principles are described.

Gazzaniga et al (Proceed. 12th Pharm. Int. Techn. Conf., 1993, 1, 400-8.) described tablets which were spray-coated or press-coated with HPMC layers to obtain delayed release preparations of ketoprofen or verapamil. The HPMC layer may also contain an insoluble filler. Gazzaniga et al have also described press-coated tablets containing antipyrine with HPMC layers to obtain delayed release, having an outer enteric coating comprising Eudragit L30D applied thereon. (Proc. Inter. Symp. Control. Rel. Bioact. Mater. 1996, 23, 571-2.)

EP-A1-0629398 describes a dosage form comprising a drug and an organic acid in a core surrounded by a film that controls the start of release, and further covered by an enteric coating layer. This dosage form is not suitable for substances that are sensitive to acidic degradation as the core comprises an organic acid.

Osmotic systems are described by Fox ("Colon-Targeted Osmotic System for Oral delivery of Peptides and Proteins", In; Oral Delivery of Proteins, Peptides and other Biopharmaceutical Agents; Proceedings Technology Management Group, Wakefield, MA, USA, Sept. 1991). A colon release system, OROS-CT, is used to obtain delayed extended release after a lag time. The dosage form had an enteric coating which dissolved in the small intestines, the drug release started after a desired lag time and the release was maintained during some hours.

EP 0384642 and EP 0384646 (as well as Pharm. J., July 27th, 1991 pp.137-9) introduced the PULSINCAPTM dosage form both for enteric coated system and non-enteric coated system. The system comprises a capsule composed of a water insoluble body and a water soluble cap. The drug formulation was contained within the capsule body and sealed
5 within this region by means of a hydrogel plug.

Conte et al (Drug Development and Industrial Pharmacy, 1989, vol 15, pp. 2583-96) described a three-layer tablet giving a double pulse system suitable for ibuprofen. The first layer contained a rapidly releasing formulation, and was separated from the layer
10 comprising the second dose by a swellable polymeric barrier layer. The second dose was coated with an impermeable film of ethyl cellulose. This construction releases the drug in an acidic medium.

A dosage form for diltiazem was described in US 5,567,441 comprising a mixture of one
15 fraction of enteric coated pellets with slow release and another fraction of delayed pulse release membrane coated pellets, the latter fraction of pellets were not enteric coated. Such a dosage form will not be suitable for acidic sensitive drugs such as omeprazole or the like.

There are two newly published patent applications which propose controlled release
20 formulations comprising a proton pump inhibitor, i.e. in WO 97/02020 a dosage form for pantoprazole in combination with an antibacterial substance is proposed. At least a part of the pantoprazole dose shall be in slow-release form with a continuous release of pantoprazole during time. The preparation has one intermediate layer which will remain intact as a layer and is releasing the dose of pantoprazole continuously so as a pantoprazole
25 plasma level persists as long as possible. WO 97/02021 discusses a very similar dosage form of a reversible proton pump inhibitor in combination with an antibacterial substance.

Detailed description of the drawings

Figures 1 - 5 show graphs illustrating the dissolution profiles for some of the inventive pharmaceutical formulations prepared in the examples. The graphs show the released amount of substance with respect to time. The amount of released substance is identified by registration of the absorbance at 292 nm in a buffer solution.

5

Figure 1 shows the dissolution profile for single dose layered pellets prepared in Example 1.

Figure 2 shows the dissolution profile for single dose layered pellets prepared in Example 2.

10 Figure 3 shows the dissolution profile for single dose layered pellets prepared in Example 3.

Figure 4 shows the dissolution profile for single dose layered tablets prepared in Example 5.

15 Figure 5 shows the dissolution profile for multiple dose layered tablets prepared in Example 6.

Summary of the invention

20 The therapeutic effect of omeprazole and similar substances may be improved by providing an extended plasma profile by once daily administration of a dosage form. The present invention obtains such an extended plasma profile by a pharmaceutical dosage form capable of releasing the drug in discrete pulses separated in time, i.e. a dosage form with a discontinuous release pattern. The present invention provides such dosage forms comprising an acid susceptible H^+K^+ -ATPase inhibitor, such as omeprazole or any other

25 proton pump inhibitor. A specific problem is that the pharmaceutical dosage forms suitable for a H^+K^+ -ATPase inhibitor must fulfill certain requirement with respect to gastric acid resistance for enteric coated articles specified in the US Pharmacopeia (Edition 23).

30 According to one aspect of the invention the extended plasma profile of a proton pump inhibitor is provided by once daily administration of a dosage form which, in the small

and/or large intestines (but not in the stomach), releases the proton pump inhibitor in two or more discrete pulses separated in time by from 0.5 up to 12 hours, preferably separated in time by from 0.5 and up to 8 hours, and more preferably by from 0.5 and up to 4 hours.

- 5 According to another aspect of the invention a discontinuous release pattern of the proton pump inhibitor by once daily administration of a dosage form is provided wherein a part of the dosage form gives a pulsed delayed release, and other parts of the dosage form release the proton pump inhibitor instantly. The dosage form provides at least two consecutive pulses for release of substance, the pulses should be separated in time by from 0.5 and up
10 to 12 hours, preferably by from 0.5 and up to 8 hours, and more preferably by from 0.5 and up to 4 hours interval.

The present pulsed release formulations show an improved patient compliance over an administration regimen comprising consecutive administration of two or more unit doses
15 within specified time intervals.

Detailed description of the invention

Active substance.

20

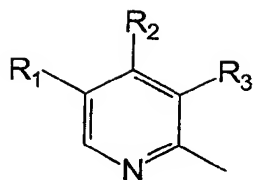
Compounds of interest for the novel pharmaceutical formulations according to the present invention are compounds of the general formula I, an alkaline salt thereof, one of the single enantiomers thereof or an alkaline salt of one of the enantiomers

25

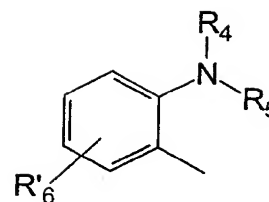


wherein

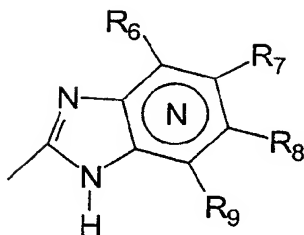
Het₁ is



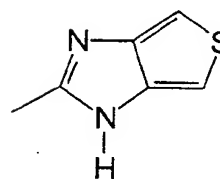
or



Het₂ is

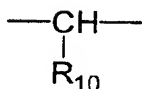


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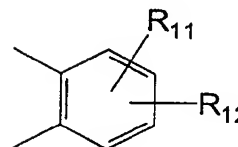


5

X =



or



wherein

- 10 N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R₆-
R₉ optionally may be exchanged for a nitrogen atom without any substituents;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy
optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino,
15 morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and arylalkyl;

R_6' is hydrogen, halogen, trifluoromethyl, alkyl or alkoxy;

R_6 - R_9 are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, halo-alkoxy, alkylcarbonyl, alkoxycarbonyl, oxazolinyl, and trifluoroalkyl, or adjacent groups

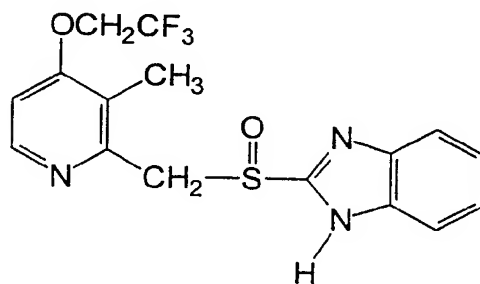
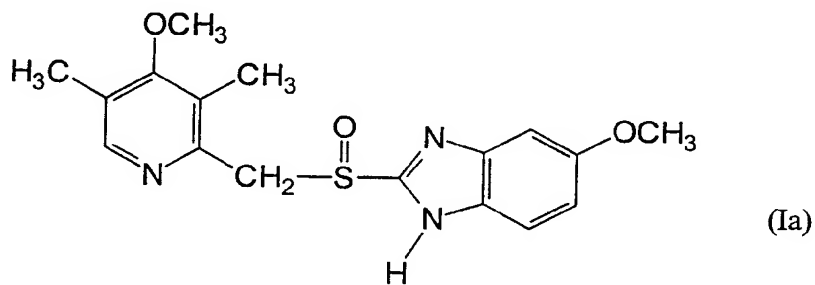
R_6 - R_9 form ring structures which may be further substituted;

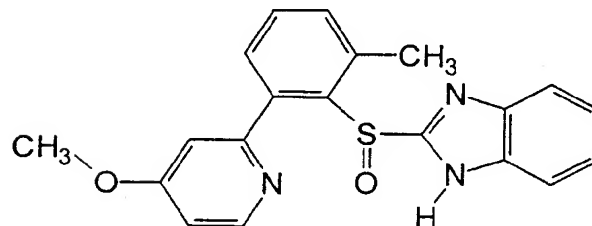
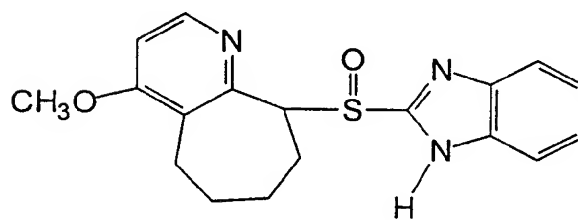
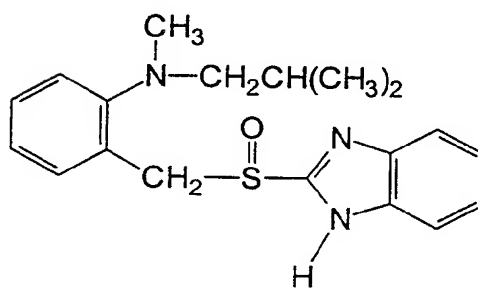
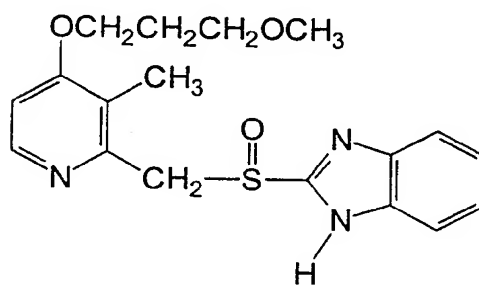
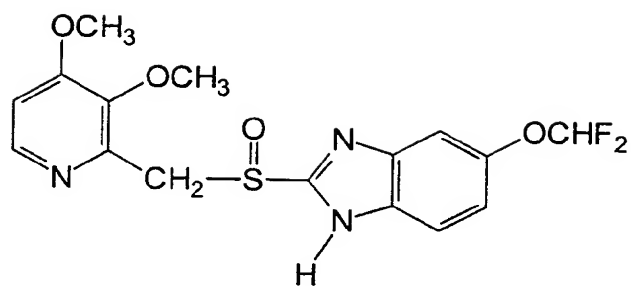
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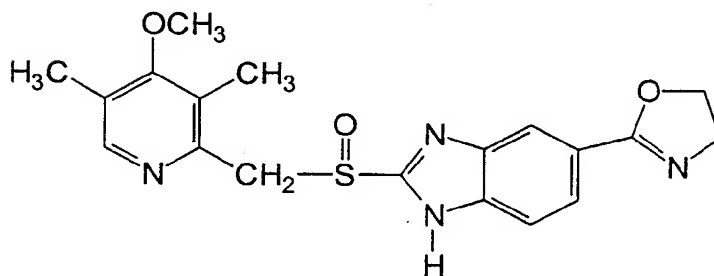
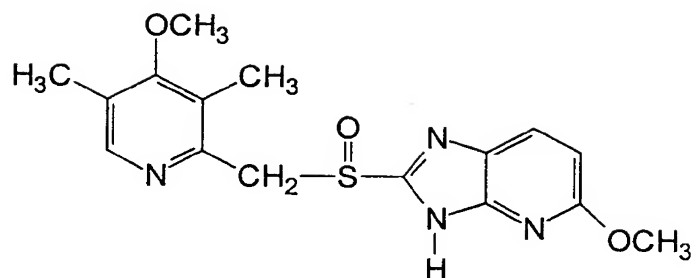
R_{10} is hydrogen or forms an alkylene chain together with R_3 and

R_{11} and R_{12} are the same or different and selected from hydrogen, halogen or alkyl.

10 Examples of specifically interesting compounds according to formula I are







5 The compound suitable to be used in the pulsed release formulations according to the present invention may be used in neutral form or in the form of an alkaline salt, such as for instance the Mg^{2+} , Ca^{2+} , Na^+ or K^+ salts, preferably the Mg^{2+} salts. The compounds may also be used in the form of one of its single enantiomers or an alkaline salt of the single enantiomer.

10

Especially preferred compounds for the oral pharmaceutical preparation according to the present invention are omeprazole, a magnesium salt of omeprazole or a magnesium salt of the (-)-enantiomer of omeprazole. Omeprazole and related substances as well as their preparations are described in EP 5129, EP 124 495, WO 95/01977, WO 94/27988 hereby
15 incorporated in a whole by references.

The above compounds are susceptible to degradation/transformation in acidic and neutral media. Generally, the degradation is catalyzed by acidic reacting compounds and the active compounds are stabilized with alkaline reacting compounds. There are different enteric
20 coating layered preparations comprising omeprazole as well as other proton pump

inhibitors described in the prior art, see for instance US-A 4,853,230, WO 95/ 01783, and WO 96/ 01623. Especially, the latter describes alternative manufacturing methods for the preparation of enteric coating layered pellets comprising omeprazole and similar compounds.

5

The dosage forms according to the invention provide at least a part of the dose with a pulsed delayed release of the drug and another part of the formulation with rapid or instant release. The instant and pulsed delayed release of the drug can be achieved according to different principles, such as

- 10 - by single dose layered pellets or tablets,
 - by multiple dose layered pellets or tablets, or
 - by two or more different fractions of single or multiple dose layered pellets or tablets, optionally in combination with pellets or tablets having instant release.

- 15 Multiple dose layered pellets, or two or more different populations of single or multiple dose layered pellets prepared according to any of the below described principles, are filled into a capsule or together with tablet excipients compressed into a multiple unit tablet. Alternatively, a multiple dose layered tablet may be prepared.

- 20 *Single dose layered pellets or tablets.*

According to one aspect of the invention, pellets or tablets giving one single delayed release pulse of the drug are prepared. The single dose layered pellets or tablets may be constructed as to comprise the following parts:

25

- a core material, optionally layered on a seed/sphere, the core material comprises the drug together with a water swellable substance, and optionally pharmaceutically acceptable excipients, and the core material is being free from acidic compounds, and thereupon the following sequence of layers:

- 30 - a surrounding lag time controlling layer, and finally

- an enteric coating layer positioned to cover the lag time controlling layer.

According to an alternative aspect of the invention, it is also possible to construct the layered pellets or tablets as to comprise the following parts:

5

- a core material, optionally layered on a seed/sphere, the core material comprises the drug optionally together with pharmaceutically acceptable excipients, and the core material is being free from acidic compounds, and thereupon the following sequence of layers:
 - a surrounding layer comprising a water swellable substance, and thereupon
 - 10 - a surrounding lag time controlling layer, and finally
 - an enteric coating layer positioned to cover the lag time controlling layer.

Multiple dose layered pellets or tablets.

- 15 According to another aspect of the invention, multiple dose layered pellets or tablets giving two or more delayed release pulses of the drug are prepared. These pellets or tablets may be constructed as to comprise the following parts:

- a core material (I), optionally layered on a seed/sphere, the core material comprises the drug together with a water swellable substance, and optionally pharmaceutically acceptable excipients, and the core material is being free from acidic compounds, and thereupon the following sequence of layers:
 - a surrounding lag time controlling layer (II), and
 - a layer (III) comprising the drug optionally together with a water swellable substance, and/or pharmaceutically acceptable excipients; the layer is being free from acidic compounds, and
 - 20 - optionally a separating layer (IV) which is water-soluble or in water rapidly disintegrating,

wherein the layers II and III and the optional layer IV may appear in repeated sequences (in this order) and each set of layers (II + III) gives an additional single pulse of the drug. The dosage form is finally covered by an outer enteric coating layer (V).

5 Thus, a three-pulsed delayed release pellet or tablet could be constructed as having the following sequence of layers I+ II + III + II + III + an optional layer IV, and the prescribed outer enteric coating layer (V).

According to an alternative aspect of the invention, the multiple dose layered pellets or
10 tablets may also be constructed with the following parts:

- a core material (I), optionally layered on a seed/sphere, the core material comprises the drug optionally together with pharmaceutically acceptable excipients, and the core material is being free from acidic compounds, and thereupon the following sequence of layers:
- 15 - a surrounding layer (II) comprising a water swellable substance, followed by
- a surrounding lag time controlling layer (III) and
- a layer (IV) comprising the drug optionally together with pharmaceutically acceptable excipients; the layer is being free from acidic compounds, and
- optionally a separating layer (V) which is water-soluble or in water rapidly disintegrating,

20

wherein the layers II, III, IV and the optional layer V may appear in repeated sequences (in this order) and each set of layers (II + III+ IV) gives an additional single pulse of the drug. The dosage form is covered by an outer enteric coating layer (VI).

25 Thus, a three-pulsed pellet or tablet could be constructed as having the following sequence of layers I+ II + III + IV+ II + III + IV + an optional layer V, and the prescribed outer enteric coating layer (VI).

The core material comprising the active drug can be prepared either by coating layering the
30 drug onto a seed, such as for instance sugar spheres, or by extrusion

/spheronization of a mixture comprising the drug and pharmaceutical acceptable excipients. It is also possible to prepare the core material by using tablet technology, i.e. compression of drug granules and optionally pharmaceutically acceptable excipients into a tablet core.

- 5 For pellets of the two types, i.e. single or multiple dose pellets, which have the drug deposited onto a seed/sphere by layering, it is also possible to have an optional layer comprising a water swellable substance beneath the drug containing layer in the core material.
- 10 The prepared core material is used for further processing. Different techniques to prepare the core material for pellets or tablets are described below.

Core material

- 15 The core material for the individual pellets or tablets can be constituted according to different principles. A seed/sphere layered with active substance, the active substance is optionally mixed with a water swellable substance and/or a pharmaceutically acceptable excipient, can be used as core material for the further processing. The core material is free from acidic compound except that the active substance as such might be slightly acidic.
- 20 The micro environment around the acid susceptible H^+K^+ -ATPase inhibitor should preferable be not less than pH=7, and more preferably not less than pH=8 when water is absorbed to the core material mixture or when water is added in small amount to the mixture.
- 25 The seeds/spheres can be water insoluble and comprise different oxides, celluloses, organic polymers and other materials, alone or in mixtures, or be water soluble and comprise different inorganic salts, sugars and other materials, alone or in mixtures. Further, the seeds/spheres may comprise active substance in the form of crystals, agglomerates, compacts etc. The size of the seeds may vary between approximately 0.1 and 2 mm. The

seeds layered with active substance are produced either by powder or solution/suspension layering using for instance granulating or spray coating/layering equipment.

Before the seeds are layered, the active substance may be mixed with further components to obtain preferred handling and processing properties and a suitable concentration of the active substance in the final mixture.

Such components can be binders, surfactants, fillers, disintegrating agents, alkaline additives or other pharmaceutically acceptable ingredients, alone or in mixtures. The binders are for example celluloses such as hydroxypropyl methylcellulose, methylcellulose, hydroxypropyl cellulose and carboxymethyl-cellulose sodium, polyvinyl pyrrolidone, gelatine, sugars, starches and other pharmaceutically acceptable substances with cohesive properties. Suitable surfactants are found in the groups of pharmaceutically acceptable non-ionic surfactants, such as polysorbate 80, or ionic surfactants such as for instance sodium lauryl sulfate.

Optionally an osmotic agent is placed in the core material. Such an osmotic agent is water soluble and will provide an osmotic pressure in the tablet. Examples of osmotic agents are magnesium sulfate, sodium chloride, lithium chloride, potassium chloride, potassium sulfate, sodium carbonate, lithium sulfate, calcium bicarbonate, sodium sulfate, calcium lactate, urea, magnesium succinate, sucrose or mixtures thereof.

Alternatively, the active substance optionally mixed with any of the components defined above can be formulated into a core material. Said core material may be produced by extrusion/spheronization, balling or compression utilizing different process equipments. For extrusion/spheronization processes incorporation of a microcrystalline cellulose and a low-substituted hydroxypropylcellulose in the core material is preferred. The size of the formulated core materials is approximately between 0.1 and 4 mm, preferably between 0.1 and 2 mm for a pellet preparation, and between 2 and 10 mm, preferably between 3 and 7 mm for a tablet preparation.

Suitable alkaline additives can be chosen among, but are not restricted to, substances such as the sodium, potassium, calcium, magnesium and aluminium salts of phosphoric acid, carbonic acid, citric acid or other suitable weak inorganic or organic acids; aluminium
5 hydroxide/sodium bicarbonate coprecipitate; substances normally used in antacid preparations such as aluminium, calcium and magnesium hydroxides; magnesium oxide or composite substances, such as $\text{Al}_2\text{O}_3 \cdot 6\text{MgO} \cdot \text{CO}_2 \cdot 12\text{H}_2\text{O}$, $(\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O})$, $\text{MgO} \cdot \text{Al}_2\text{O}_3 \cdot 2\text{SiO}_2 \cdot n\text{H}_2\text{O}$ or similar compounds; organic pH-buffering substances such as trihydroxymethylaminomethane, basic amino acids such as arginine, and their salts or other
10 similar, pharmaceutically acceptable pH-buffering substances.

Alternatively, the aforementioned core material for a pellet preparation can be prepared by using spray drying or congealing techniques.

15 *Swelling layer.*

The applied swelling layer comprises one or more water swellable substances, a suitable binder, and optionally pharmaceutically acceptable excipient(s). Suitable swellable substances, binders, as well as pharmaceutically acceptable excipients are described below.
20 The swelling layer expands when exposed for an aqueous solution such as intestinal fluid.

Alternatively, one of the additional drug containing layers applied onto the core material may be a combined drug swelling layer.

25 *Water swellable substances.*

Water swellable substances suitable for the dosage forms according to the present invention are compound which are able to expand when they are exposed to an aqueous solution, such as intestinal fluid.

One or more water swellable substances may be present in the core material together with the active substance and optionally pharmaceutically acceptable excipient(s). Alternatively, one or more water swellable substances are included in a swelling layer applied onto the
5 core material. As a further alternative, swellable substance(s) they may also be present in an optional swelling layer situated beneath the drug containing layer, if a layered seed or sphere is used as the core material.

The amount and art of water swellable substance(s) in the swelling layer or in the core
10 material is chosen in such a way that the core material or the swelling layer in contact with an aqueous solution, such as intestinal fluid, will expand to such a degree that the surrounding lag-time controlling membrane ruptures. A water swellable substance may also be included in the drug comprising layer of the multiple layered pellets or tablets to increase dissolution rate of the drug fraction.

15

Suitable substances which can be used as water swellable substances are for instance, low-substituted hydroxypropyl cellulose, e.g. L-HPC; cross-linked polyvinyl pyrrolidone (PVP-XL), e.g. KollidonTM CL and PolyplasdoneTM XL; cross-linked sodium
carboxymethylcellulose, e.g. Ac-di-solTM, PrimelloseTM; sodium starch glycolate, e.g.
20 PrimojelTM; sodium carboxymethylcellulose, e.g. Nymcel ZSB 10TM; sodium carboxymethyl starch, e.g. ExplotabTM; ion-exchange resins, e.g. DowexTM or AmberliteTM; microcrystalline cellulose, e.g. AvicelTM; starches and pregelatinized starch, e.g. Starch 1500TM, Sepistab ST200TM; and formalin-casein, e.g. Plas-VitaTM. One of these substances
25 can be used or any combinations or mixtures thereof, taking into consideration that the use of any acidic compound not is suitable.

Lag time controlling layer.

The lag time controlling layer is a semipermeable membrane comprising a water resistant polymer that is semipermeable for an aqueous solution, such as intestinal fluid. Suitable polymers are cellulose acetate, ethylcellulose, polyvinyl acetate, cellulose acetate butyrate, cellulose acetate propionate, acrylic acid copolymers, such as EudragitTM RS or RL. The
5 polymer may optionally comprise pore forming agents, such as a water soluble substance, eg. sucrose, salt; or a water soluble polymer eg. polyethylene glycol. Also pharmaceutically acceptable excipients such as fillers and membrane strength influencing agents such as talc, aerosil, or sodium aluminium silicate may be included.

10 There is at least one lag time controlling layer present in the dosage forms according to the invention. The lag time controlling layer positioned nearest the inner core material is constructed in the form of a semipermeable membrane that will disrupt after a desired time after ingestion.

15 A desired lag time may be adjusted by the composition and thickness of the layer. The amount of substances forming such a disrupting semipermeable membrane, i.e. a lag time controlling layer, is usually in the range from 0.5 to 25 % counted on the weight of the core material including swelling substances or a swelling layer. Preferably the amount of such a lag time controlling layer, i.e. a disrupting semipermeable membrane, is between 2 to 20
20 % by weight.

A preferred disrupting semipermeable membrane, i.e. lag time controlling layer, is composed of a mixture of ethylcellulose and talc. The mixture contains most preferably 10 to 80 % w/w of talc.

25

Optionally, any additional lag time controlling layer may be constructed as a disrupting semipermeable membrane.

Enteric coating layer(s) and separating layer(s).

30

Before applying an enteric coating layer onto the layered pellets or tablets, they may optionally be covered with one or more separating layers comprising pharmaceutical excipients optionally including alkaline compounds such as for instance pH-buffering compounds. This separating layer separates the composition of the layered pellets or tablets
5 from the outer enteric coating layer.

The separating layer as well as the other type of layers, such as the swelling and lag time controlling layers, can be applied by coating or layering procedures in suitable equipments such as coating pan, coating granulator, centrifugal granulator or in a fluidized bed
10 apparatus (including Wurster type) using water and/or organic solvents for the coating process. As an alternative the layer(s) can be applied by using powder coating or press-coating techniques.

Suitable materials for the optional separating layer are pharmaceutically acceptable
15 compounds such as, for instance, sugar, polyethylene glycol, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, methylcellulose, ethylcellulose, hydroxypropyl methylcellulose, carboxymethylcellulose sodium and others, used alone or in mixtures. Additives such as plasticizers, colorants, pigments, fillers, anti-tacking and anti-static agents, such as for instance magnesium stearate, titanium dioxide,
20 talc, pH-buffering substances and other additives may also be included into the separating layer.

When the optional separating layer is applied to the layered pellets or tablets it may constitute a variable thickness. The maximum thickness of the optional separating layer is
25 normally only limited by processing conditions. The separating layer may serve as a diffusion barrier and may act as a pH-buffering zone. The optional separating layer may improve the chemical stability of the active substance and/or the physical properties of the dosage form.

30 Finally the layered pellets or tablets are covered by one or more enteric coating layers by using a suitable coating technique. The enteric coating layer material may be dispersed or

dissolved in either water or in suitable organic solvents. As enteric coating layer polymers one or more, separately or in combination, of the following can be used; e.g. solutions or dispersions of methacrylic acid copolymers, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate, polyvinyl acetate phthalate, cellulose acetate trimellitate, carboxymethyl ethylcellulose, shellac or other suitable enteric coating layer polymer(s).

Additives such as dispersants, colorants, pigments, additional polymers e.g. poly(ethylacrylat, methylmethacrylat), anti-tacking and anti-foaming agents may also be included into the enteric coating layer. Other compounds may be added to increase film thickness and to decrease diffusion of acidic gastric juices into the acid susceptible material. The enteric coating layer(s) constitutes a thickness of approximately at least 10 μm , preferably more than 20 μm . The maximum thickness of the applied enteric coating layer(s) is normally only limited by processing conditions.

Any of the applied polymer containing layers, and specially the enteric coating layers may also contain pharmaceutically acceptable plasticizers to obtain desired mechanical properties. Such plasticizers are for instance, but not restricted to, triacetin, citric acid esters, phthalic acid esters, dibutyl sebacate, cetyl alcohol, polyethylene glycols, glycerol monoesters, polysorbates or other plasticizers. The amount of plasticizer is preferably optimized for each formula, in relation to the selected polymer(s), selected plasticizer(s) and the applied amount of said polymer(s).

Final dosage form

The prepared layered pellets, optionally mixed with tablet excipients are filled into a capsule, or compressed into a multiple unit tableted dosage form. Alternatively, the dosage form is a multiple layered tablet. Prepared tablets are optionally covered with filmforming agent(s) to obtain a smooth surface of the tablet and further enhance the stability of the tablet during packaging and transport. Such a tablet coating layer may further comprise

additives like anti-tacking agents, colorants and pigments or other additives to obtain a tablet of good appearance.

The dosage forms according to the invention are suitable for oral administration. The dose will depend on the nature and severity of the disease to be treated. The dose may also vary according to the age, body weight, and response of the individual patient. Children and patients with liver diseases as well as patients under long term treatment will generally benefit from doses that are somewhat lower than the average. In the treatment of other conditions higher doses than average will be used.

Preferably, a dosage form of the proton pump inhibitor, for instance 1 - 500 mg is administered once a day. Suitable doses comprise for instance about 5 - 100 mg of the substance, and more preferably 10 - 80 mg. The dosage form may be administered together with other suitable drugs, such as antibacterial compound(s), NSAID(s), motility stimulating agents, and/or antacids.

Examples

The following examples describe the invention more in detail without restricting it.

Example 1.

Pulsed single dose delayed release layered pellets comprising magnesium salt of S-omeprazole (pellet strength approx. 44 mg/g).

Preparation of core material (spheres layered with drug).

A drug containing suspension was made according to the composition below;

S-omeprazole Mg-salt	100g
HPMC, 6 cps	15 g

Polysorbate 80	2 g
Purified water	323 g

HPMC was dissolved in water during stirring with subsequent addition of Polysorbate 80 and the drug. The suspension was sprayed onto 290 g of sugar spheres (Non-pareil) in a fluidized bed. The weight of the obtained product was 395 g.

5

Application of a swelling layer

A (water free) suspension containing in water swellable substances was prepared according to the following composition;

Low-substituted hydroxypropylcellulose (L-HPC)	162 g
Hydroxypropylcellulose LF (HPC-LF)	74 g
Talc	354 g
EtOH (99.5%)	3100 g

10

HPC-LF was dissolved in ethanol during stirring, then talc and swelling agent L-HPC was added. The suspension was sprayed onto 175 g of the core material from above in a Wurster equipped fluidized bed. The weight of the obtained product was 711 g.

15 Application of lag time controlling layer (semipermeable membrane).

A coating suspension was made according to the following formula;

Ethylcellulose, 10 cps	10 g
Talc	23 g
EtOH (99.5%)	1000 g

The ethylcellulose was dissolved in the ethanol during stirring, then talc was added.

20 Spraying of the suspension onto 150 g of swelling layered pellets from above (0.61- 0.71

mm obtained by sieving) was done in a Wurster equipped fluidized bed. The weight of the obtained pellets was 176 g.

Pellets (corresponding to approx. 10 mg active substance) were analyzed using USP dissolution apparatus No. 2 (paddle), and operated at 100 rpm, 37°C and with a phosphate buffer pH 6.8. The dissolution of active substance was followed by registration of the absorbance at 292 nm in a buffer solution, using a 0.5 cm flow-through compact cell. The dissolution profile measured at 292 nm is shown in Figure 1.

Example 2.

Pulsed single dose delayed release layered pellets comprising magnesium salt of S-omeprazole (pellet strength approx. 43 mg/g).

Preparation of core material (spheres layered with drug)

A drug containing suspension was made according to the composition below;

S-omeprazole Mg-salt	100g
HPMC, 6 cps	15 g
Polysorbate 80	2 g
Purified water	323 g

HPMC was dissolved in water during stirring with subsequent addition of Polysorbate 80 and the substance. The suspension was sprayed onto 290 g of sugar spheres (Non-pareil) in a fluidized bed. After coating the weight of the obtained product was 395 g.

Application of swelling layer

A water free suspension containing in water swellable substances was prepared according to the following composition;

Low-substituted hydroxypropylcellulose (L-HPC)	162 g
Hydroxypropylcellulose LF (HPC-LF)	74 g
Talc	354 g
EtOH (99.5%)	3100 g

HPC-LF was dissolved in ethanol during stirring, then talc and swelling agent L-HPC was added. The suspension was sprayed onto 175 g pellets from above in a Wurster equipped fluidized bed. The weight of the obtained product was 711 g.

5

Application of lag time controlling layer (semipermeable membrane).

100 g of the swelling layered pellets obtained above were coated to obtain a lag-time controlling layer with the suspension below;

Ethylcellulose, 10 cps	8 g
Talc	9 g
Mg-Stearate	2 g
EtOH (99.5%)	620 g

10

The suspension was prepared by dissolving the ethylcellulose in the ethanol during stirring, then the other compounds were added. Spraying of the suspension onto the pellets was done in a Wurster equipped fluidized bed. The weight of the obtained pellets was 116 g.

15 The pellets were analyzed as is described in Example 1. The dissolution profile is shown in Figure 2.

Example 3.

20 Single dose layered pellets, i.e. enteric coated pulsed single dose delayed release pellets comprising magnesium salt of S-omeprazole (pellet strength approx. 37 mg/g).

Application of enteric coating layer.

Pellets from Example 1 were enteric coated in a fluidized bed with a coating dispersion according to below;

Eudragit L30 D-55 (30 % w/w dispersion)	73.3g
Triethylcitrate (TEC)	6.6 g
Glycerole monostearate (GMS)	0.3 g
Polysorbate 80	0.03 g
Purified water	40.4 g

5

A homogenous coating dispersion was prepared by dispersing polysorbate 80 and glycerol monostearate in water. Triethylcitrate was dissolved in the Eudragit dispersion and thereafter the two dispersions were mixed to obtain the coating dispersion.

- 10 The coating dispersion was applied onto 120 g pellets from Example 1, using a Wurster equipped fluidized bed. The weight of the layered pellets was 140 g.

Pellets (corresponding to approx. 10 mg active substance) were analyzed using USP dissolution apparatus No. 2 (paddle) and operated at 100 rpm and 37°C. First the pellets
15 were immersed in 0.1M HCl for 2 hours (pH 1.2), thereafter phosphate buffer components were added to obtain pH 6.8. The dissolution profile was registered as described in example 1, and is shown in Figure 3. The pellets were examined with respect to acid resistance. After exposure to 0.1 M HCl during two hours, 96 % of the active substance remained intact.

20 Example 4.

Single dose layered pellets, i.e. enteric coated pulsed single dose delayed release pellets comprising magnesium salt of omeprazole (pellet strength approx. 35 mg/g.).

Preparation of core material (spheres layered with drug).

A drug containing suspension was made according to the composition below;

Omeprazole Mg-salt	100 g
HPMC, 6 cps	15 g
Polysorbate 80	2 g
Purified water	323 g

- 5 HPMC was dissolved in the water during stirring with subsequent addition of Polysorbate 80 and the drug. The suspension was sprayed onto 290 g of sugar spheres (Non-pareil) in a fluidized bed. After the coating the weight of the obtained product was 395 g.

Application of swelling layer

- 10 A (water free) suspension containing in water swellable substances was prepared according to the following composition;

Low-substituted hydroxypropylcellulose (L-HPC)	162 g
Hydroxypropylcellulose LF (HPC-LF)	74 g
Talc	354 g
EtOH (99.5%)	3100 g

- 15 HPC-LF was dissolved in ethanol during stirring, then the talc and the swelling agent L-HPC was added. The suspension was sprayed onto 175 g of core material from above in a Wurster equipped fluidized bed. The weight of the obtained product was 711 g.

Application of lag time controlling layer (semipermeable membrane).

- 20 120 grams of the swelling layered pellets (the fraction 0.61 mm - 0.71 mm obtained by sieving) obtained above were coated with the suspension below;

Ethylcellulose, 10 cps 8 g

Talc	18 g
EtOH (99.5%)	810 g

The suspension was prepared by dissolving ethylcellulose in ethanol during stirring, then talc was added. The suspension was sprayed onto the pellets in a Wurster equipped fluidized bed. The weight of the obtained product was 137 g.

5

Application of enteric coating layer .

120 grams of the pellets from the previous step above were coated with an enteric coating solution according to below;

HPMCP (HP-55)	33 g
Cetanol	2.4 g
Acetone	353 g
EtOH (99.5%)	151 g

10

The coating solution was prepared by dissolving HPMCP and cetanol in a mixture of the solvents during stirring. The coating solution was applied in a Wurster equipped fluidized bed. The weight of the layered pellets was 149 g.

- 15 The layered pellets were examined with respect to acid resistance in 0.1 M HCl. The acid resistance was 97 %.

Example 5.

- 20 Single dose layered tablets, i.e. enteric coated pulsed single dose delayed release tablets comprising magnesium salt of S-omeprazole (Tablet strength approx. 16 mg).

Granules

Granules for homogenous tablet cores were made according to the following composition;

S-omeprazole Mg-salt	229 g
Microcrystalline cellulose, Avicel pH 101	151 g
Microcrystalline cellulose, Avicel PH 102 sp. coarse grade	400 g
L-HPC	256 g
PVP-XL	302 g
Sodium laurylsulphate (SLS)	30 g
Water purified	1060 g

A granulating solution was prepared by dissolving the SLS in 460 g of purified water.

The powders above were mixed in a mixer after which the solution was added in an even
5 stream. Thereafter approx. 600 g water was added during continued mixing, to give
satisfactory consistency to the mass.

The mass was dried in a drying oven at 50°C over night.

10 Preparation of tablet cores

After milling through a 1.0 mm screen the obtained granules were mixed with tablet
lubricant, sodium chloride, and an additional amount of swellable substance, according to
the following composition;

Granules for tablet core	400 g
Sodium chloride (passing 0.3mm)	80 g
Sodium stearyl fumarate (Pruv®)	8 g
Polyvinyl pyrrolidone cross-linked (PVP-XL)	20 g

15

The mixing was performed to homogeneity in a Kenwood mixer .

The mixture was compressed to 6 mm in diameter tablets having an average weight of 126
mg, on a single punch tableting machine (Diaf).

Application of lag time controlling layer (semipermeable membrane).

The tablets from previous step were coated in a Wurster equipped fluidized bed coating apparatus with a coating suspension of the following composition;

5

EtOH 99.5% (w/v)	291 parts by weight
Ethyl cellulose N-10	11 parts by weight
Talc, micronized	7 parts by weight
Sum:	309 parts.

200 grams of tablets were processed and the coating was continued until the average tablet weight was 134 mg.

10 Application of enteric coating layer

The tablets obtained in the previous step were coated with an enteric coating layer in the same equipment as for the preceding coating step. The coating solution had the following composition;

Hydroxypropyl methylcellulose phtalate (HP-55®)	16 parts by weight
Cetanol	1 - “ -
Acetone	151 - “ -
Ethanol (95% w/v)	65 - “ -
Sum:	233 parts

15

100 grams of the tablets were processed and the coating was continued until the average tablet weight was 148 mg.

Individual tablets were analyzed using USP dissolution apparatus No. 2 (paddle) equipped
20 with stationary baskets and operated at 100 rpm and 37°C. First the tablets were pre-

exposed for 0.1 M HCl for two hours (pH 1.2), whereafter the dissolution medium was changed to phosphate buffer pH 6.8.

The dissolution profile obtained was registered as described in example 1, and can be seen in Figure 4.

Example 6.

Multiple dose layered tablets, i.e. enteric coated dual pulsed multiple release tablets. (tablet strength approx. 2 x 15 mg).

Granules

Granules for tablet cores were made according to the following composition;

S-omeprazole Mg-salt	229 g
Microcrystalline cellulose, Avicel PH 101	151 g
Microcrystalline cellulose, Avicel PH 102 sp. Coarse grade	400 g
L-HPC	256 g
PVP-XL	302 g
Sodium laurylsulphate (SLS)	30 g
Water purified	1060 g

A granulating solution was prepared by dissolving the SLS in 460 g of purified water.

The powders above were mixed in a mixer after which the solution was added in an even stream. Thereafter approx. 600 g water was added during continued mixing, to give satisfactory consistency to the mass.

The mass was dried in a drying oven at 50°C over night.

Preparation of tablet cores

After milling through a 1.0 mm screen the obtained granules were mixed with tablet lubricant, sodium chloride, and an additional amount of swellable substance, according to the following composition;

5

Granules for homogenous tablet core	400
Sodium chloride (passing 0.3mm)	80
Sodium stearyl fumarate (Pruv®)	8
Polyvinyl pyrrolidone cross-linked (PVP-XL)	20

The mixing was performed to homogeneity in a Kenwood mixer .

The mixture was compressed to 6 mm in diameter tablets having an average weight of 126 mg, on a single punch tableting machine (Diaf).

10

Application of lag time controlling layer (semipermeable membrane).

The tablets from previous step were coated in a Wurster equipped fluidized bed coating apparatus with a coating suspension of the following composition;

15

EtOH 99.5% (w/v)	291 parts by weight
Ethyl cellulose N-10	11 parts by weight
Talc, micronized	7 parts by weight
Sum:	309 parts.

200 grams of tablets were processed and the coating was continued until average tablet weight was 134 mg.

20 Application of a drug comprising layer

The tablets obtained in previous step were coated in the same equipment as above with a coating suspension of the following composition;

S-omeprazole Mg-salt	20	parts by weight
Hydroxypropyl methylcellulose 6 cps	13	parts by weight
Ethanol 99%	128	parts by weight
Water purified	128	parts by weight
Sum:	289	parts.

99 grams of tablets were processed and the coating was continued until the average tablet weight was 162 mg.

5

Application of enteric coating layer

The tablets obtained in previous step were coated with an enteric coating layer in the same equipment as for the preceding coating step. The coating solution had the following composition;

10

Hydroxypropyl methylcellulose phthalate (HP-55)	16	parts by weight
Cetanol	1	- " -
Acetone	153	- " -
Ethanol (95% w/v)	65	- " -
Sum:	235	parts

119 grams of the tablets were processed and the coating was continued until the average tablet weight was 173 mg.

15 Individual tablets were analyzed using USP dissolution apparatus No. 2 (paddle) equipped with stationary baskets and operated at 100 rpm and 37°C. First the tablets were pre-exposed for 0.1 M HCl for two hours, whereafter the dissolution medium was changed to phosphate buffer pH 6.8.

The dissolution profile obtained was registered as described in example 1, and can be seen in Figure 5. The acid resistance of the tablets were examined and the result was 98 %.

Example 7

- 5 Multiple dose capsule formulation comprising (2 x 20) mg of omeprazole in the form of enteric coated pellets, mixed with an enteric coated tablet with delayed release.

Suspension layering

	Magnesium omeprazole	5 kg
10	Sugar spheres cores (0.25-0.355 mm diam.)	10 kg
	Hydroxypropyl methylcellulose	0.8 kg
	Water purified	20 kg

Separating layer

15	Drug containing cores (acc. to above)	14.6 kg
	Hydroxypropyl cellulose	1.5 kg
	Talc	2.5 kg
	Magnesium Stearate	0.2 kg
	Water purified	29 kg

20

Enteric coating

	Pellets (acc. to above)	9 kg
	Methacrylic acid copolymer (30% suspension)	15 kg
	Triethyl citrate	1.4 kg
25	Mono- and diglycerides (NF)	0.2 kg
	Polysorbate 80	0.02 kg
	Water purified	9 kg

Over-coating

30	Enteric coated pellets	9 kg
----	------------------------	------

Hydroxypropyl methylcellulose	0.2 kg
Mg-Stearate	0.005 kg
Water purified	3.6 kg

5

Suspension layering was performed in a fluid bed apparatus. Magnesium omeprazole was sprayed onto inert sugar sphere cores from a water suspension containing the dissolved binder.

10 The prepared core material was sub-coated in a fluid bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate.

The enteric coating consisting of methacrylic acid copolymer, mono- and diglycerides, triethylcitrate and polysorbate was sprayed onto the sub-coated pellets in a fluid bed apparatus. In the same type of apparatus the enteric coated pellets were coated with
15 hydroxypropyl methylcellulose/Mg-Stearate suspension. The over-coated pellets were classified by sieving, to pass 0.71 mm.

The product was analyzed and found to contain 209 mg/g Mg-omeprazole.

20 Single dose layered tablets, i.e. enteric coated delayed release tablets comprising magnesium salt of omeprazole. (Tablet strength approx. 16 mg.)

Granules

Granules for tablet cores were made according to the following composition (parts by weight);

Omeprazole Mg-salt	229 g
Microcrystalline cellulose, Avicel PH 101	145 g
Microcrystalline cellulose, Avicel PH 102 sp. coarse grade	400 g
L-HPC	251 g
PVP-XL	302 g
Hydroxy methylcellulose 6 cps	11 g
Sodium laurylsulphate (SLS)	30 g
Water purified	960 g

5

A granulating solution was prepared by dissolving the SLS in 460 g of purified water.

The powders above were mixed in a mixer after which the solution was added in an even stream. Thereafter approx. 500 g water was added during continued mixing, to give

10

satisfactory consistency to the mass.

The mass was dried in a drying oven at 50°C over night.

Preparation of tablet cores15

After milling through a 1.0 mm screen the obtained granules were mixed with tablet lubricant, sodium chloride and an additional amount of swellable substance, according to the following composition;

Granules for tablet core	400 g
Sodium chloride (passing 0.3mm)	80 g
Sodium stearyl fumarate (Pruv®)	8 g
Polyvinyl pyrrolidone cross-linked (PVP-XL)	20 g

The mixing was performed to homogeneity in a Kenwood mixer.

The mixture was compressed to 6 mm in diameter tablets having an average weight of 126 mg, on a single punch tableting machine (Diaf).

Application of lag time regulating layer (semipermeable membrane).

The tablets from previous step were coated in a Wurster equipped fluidized bed coating apparatus with a coating suspension of the following composition;

10

EtOH 99.5% (w/v)	291 parts by weight
Ethyl cellulose N-10	11 parts by weight
Talc, micronized	7 parts by weight
Sum:	309 parts.

200 grams of tablets were processed and the coating was continued until the average tablet weight was 134 mg.

15 Application of enteric coating layer

The tablets obtained in previous step were coated with an enteric coating layer in the same equipment as for the preceding coating step. The coating solution had the following composition;

Hydroxypropyl methylcellulose phtalate (HP-55®)	16	parts by weight
Cetanol	1	- “ -
Acetone	151	- “ -
Ethanol (95% w/v)	65	- “ -
Sum:	233	parts

20

100 grams of the tablets were processed and the coating was continued until the average tablet weight was 148 mg.

Filling of capsule

5

0.10 g of the pellets prepared above and one of the layered tablets obtained above were filled in a hard gelatine capsule size 1.

The best mode to practice the invention is according to the description given in Example 6.

10

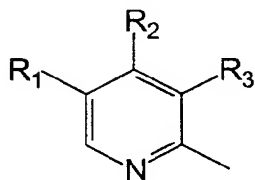
Patent claims:

1. An enteric coated pharmaceutical dosage form giving a discontinuous release of a H^+ , K^+ -ATPase inhibitor, characterized in that the release of the H^+K^+ -ATPase inhibitor is in the form of at least two consecutive pulses separated in time by from 0.5 and up to 12 hours, and at least one fraction of the dosage form has a pulsed delayed release and another fraction has instant release, and the H^+ , K^+ -ATPase inhibitor is a compound with the formula I, an alkaline salt of compound I, a single enantiomer of compound I or an alkaline salt of the single enantiomer of compound I

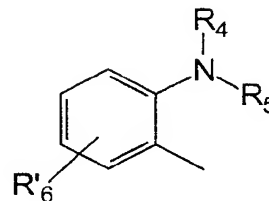


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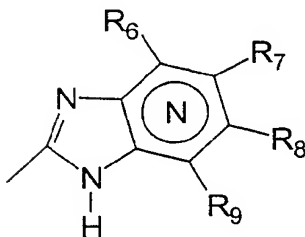
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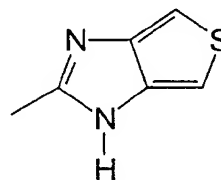
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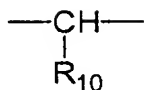
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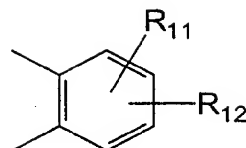
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X =



or



wherein

- 5 N in the benzimidazole moiety means that one of the ring carbon atoms substituted by R₆-R₉ optionally may be exchanged for a nitrogen atom without any substituents;

R₁, R₂ and R₃ are the same or different and selected from hydrogen, alkyl, alkoxy optionally substituted by fluorine, alkylthio, alkoxyalkoxy, dialkylamino, piperidino,
10 morpholino, halogen, phenyl and phenylalkoxy;

R₄ and R₅ are the same or different and selected from hydrogen, alkyl and arylalkyl;

R₆' is hydrogen, halogen, trifluoromethyl, alkyl or alkoxy;

- 15 R₆-R₉ are the same or different and selected from hydrogen, alkyl, alkoxy, halogen, haloalkoxy, alkylcarbonyl, alkoxy carbonyl, oxazolinyl, and trifluoroalkyl, or adjacent groups R₆-R₉ form ring structures which may be further substituted;

R₁₀ is hydrogen or forms an alkylene chain together with R₃ and

20

R₁₁ and R₁₂ are the same or different and selected from hydrogen, halogen or alkyl.

2. A dosage form according to claim 1 characterized in that the H⁺, K⁺-ATPase inhibitor is omeprazole, an alkaline salt of omeprazole, the (-)-enantiomer of omeprazole or an
25 alkaline salt of the (-)-enantiomer of omeprazole.

3. A dosage form according to claim 2, characterized in that the alkaline salt is a magnesium salt.

5 4. A dosage form according to claim 1 characterized in that the H^+ , K^+ -ATPase inhibitor is lansoprazole, alkaline salts thereof, a single enantiomer thereof or an alkaline salt thereof.

10 5. A dosage form according to any of claims 1-4 characterized in that it comprises

a) a core material comprising one portion of the H^+ , K^+ -ATPase inhibitor, a water swellable substance, and optionally pharmaceutically acceptable excipients,

b) the following sequence of layers, covering the core material

15 b1) a lag time controlling layer,

b2) at least an additional layer comprising the second portion of the H^+ , K^+ -ATPase inhibitor, and

b3) an enteric coating layer.

20 6. A dosage form according to any of claims 1-4 characterized in that it comprises

a) a core material comprising one portion of the H^+ , K^+ -ATPase inhibitor and optionally pharmaceutically acceptable excipients,

25 b) the following sequence of layers, covering the core material

b1) a swelling layer comprising a water swellable substance,

b2) a lag time controlling layer,

b3) at least an additional layer comprising the second portion the H^+ , K^+ -ATPase inhibitor, and

b4) an enteric coating layer.

7. A dosage form according to any of claims 1-4 characterized in that it comprises at least two populations of pellets or tablets or any combinations thereof, characterized in that
5 it comprises

a) the first population which has a core material comprising one portion of the H^+ , K^+ -ATPase inhibitor, a water swellable substance, and optionally pharmaceutically acceptable excipients, and wherein the core material is covered by a lag time controlling layer and an
10 enteric coating layer, and

b) the second population of pellets or tablets which has a core material comprising the second portion of the H^+ , K^+ -ATPase inhibitor and optionally pharmaceutically acceptable excipients, and the second core material is covered by an enteric coating layer.
15

8. A dosage form according to any of claims 1-4 characterized in that it comprises at least two populations of pellets or tablets or any combinations thereof, characterized in that

a) the first population comprises a core material comprising one portion of the H^+ , K^+ -ATPase inhibitor and optionally pharmaceutically acceptable excipients, wherein the core material is covered by a swelling layer comprising a water swellable substance, a lag time controlling layer and an enteric coating layer, and
20

b) the second population of pellets or tablets has a core material comprising a second
25 portion of the H^+ , K^+ -ATPase inhibitor and optionally pharmaceutically acceptable excipients, and the second core material is covered by an enteric coating layer.

9. A dosage form according to any of claims 7 and 8 characterized in that one or more additional layer comprising an additional portion of the H^+, K^+ -ATPase inhibitor is applied under the enteric coating layer of the first population a).
- 5 10. A dosage form according to any of the claims 1-9 characterized in that the two portions of the H^+, K^+ -ATPase inhibitor are released as two discrete pulses separated in time by from 0.5 and up to 4 hours.
11. A dosage form according to any of claims 5-10, characterized in that the H^+, K^+ -
10 ATPase inhibitor further comprises an admixture of an alkaline additive.
12. A dosage form according to any of claims 5-10 characterized in that the water swellable substance is selected from the group of low-substituted hydroxypropyl cellulose, cross-linked polyvinyl pyrrolidone, cross-linked sodium carboxymethyl cellulose and
15 sodium starch glycolate.
13. A dosage form according to any of claims 5 - 10 characterized in that the lag time controlling layer comprises a water resistant membrane which is semipermeable for an aqueous solution, such as intestinal fluid.
20
14. A dosage form according to claim 13, characterized in that the lag time controlling layer is a disrupting semipermeable membrane.
15. A dosage form according to claim 13 characterized in that the weight of the lag time
25 controlling layer constitutes from 0.5 to 25 % counted on the weight of the core material including water swelling substances or a swelling layer.
16. A dosage form according to any of claims 7-10 characterized in that the two or more populations of pellets or tablets or any combinations thereof are filled in a capsule.

17. A dosage form according to any of claims 7 - 10 characterized in that two or more populations of pellets with different release pattern of the H^+ , K^+ -ATPase inhibitor are mixed together with pharmaceutically acceptable excipients and compressed into a multiple unit tableted dosage form.

18. A dosage form according to any of claims 5 - 10 characterized in that a separating layer is present beneath the enteric coating layer.

19. A dosage form according to any of claims 5 - 10 characterized in that the core material comprises a seed layered with the H^+ , K^+ -ATPase inhibitor.

20. A layered pellet or tablet for the dosage form defined in any of claims 1-6 characterized in that the pellet or tablet comprises a core material comprising one portion of the H^+ , K^+ -ATPase inhibitor, a water swellable substance and optionally pharmaceutically acceptable excipients, wherein the core material is covered by a lag time controlling layer and an enteric coating layer, optionally at least one an additional layer comprising an additional portion of the H^+ , K^+ -ATPase inhibitor is applied under the enteric coating layer.

20

21. A layered pellet or tablet for the dosage form defined in any of claims 1-6 characterized in that the pellet or tablet comprises a core material comprising one portion of the H^+ , K^+ -ATPase inhibitor and optionally pharmaceutically acceptable excipients, the core material is covered by a swelling layer comprising water swellable substances, a lag time controlling layer and an enteric coating layer, optionally at least one an additional layer comprising an additional portion of the H^+ , K^+ -ATPase inhibitor is applied under the enteric coating layer.

25

22. A process for the preparation of an enteric coated dosage form comprising a H^+ , K^+ -ATPase inhibitor in which dosage form the inhibitor compound is present in at least two portions giving a release of the H^+ , K^+ -ATPase inhibitor in at least two separate pulses, which process comprises the following steps:

5

a) a core material is shaped comprising one portion of the H^+ , K^+ -ATPase inhibitor, a water swellable substance, and optionally pharmaceutically acceptable excipients,

b) the core material is layered with the following layers:

10

b1) a lag time controlling layer,

b2) a layer comprising the second portion of the H^+ , K^+ -ATPase inhibitor, and

b3) the enteric coating layer.

15

23. A process for the preparation of an enteric coated dosage form comprising a H^+ , K^+ -ATPase inhibitor in which dosage form the inhibitor compound is present in at least two portions giving a release of the H^+ , K^+ -ATPase inhibitor in at least two separate pulses, which process comprises the follow steps:

20

a) a core material is shaped comprising one portion of the H^+ , K^+ -ATPase inhibitor optionally mixed with pharmaceutically acceptable excipients,

b) the core material is layered with the following layers:

25

b1) a swelling layer comprising a water swellable substance,

b2) a lag time controlling layer,

b3) a layer comprising the second portion of the H^+ , K^+ -ATPase inhibitor, and

b4) the enteric coating layer.

24. A process for the preparation of a dosage form according to any of claims 22 or 23, wherein an additional layer comprising the H^+, K^+ -ATPase inhibitor is applied before the enteric coating layer is applied.

5 25. An enteric coated pharmaceutical dosage form according to any of claims 1-19 for use in medicine.

26. Use of an enteric coated pharmaceutical dosage form as defined in any of claims 1 - 19 in the manufacture of a medicament with improved inhibition of gastric acid secretion.

10

27. Use of an oral pharmaceutical dosage form as defined in any of claims 1 - 19 in the manufacture of a medicament with improved therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion.

15 28. A method for improving inhibition of gastric acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical dosage form as defined in any of claims 1 - 19.

20 29. A method for improving the therapeutic effect in the treatment of gastrointestinal disorders associated with excess acid secretion which comprises administering to a patient in need thereof, an oral pharmaceutical dosage form as defined in any of claims 1 - 19.

Fig. 1

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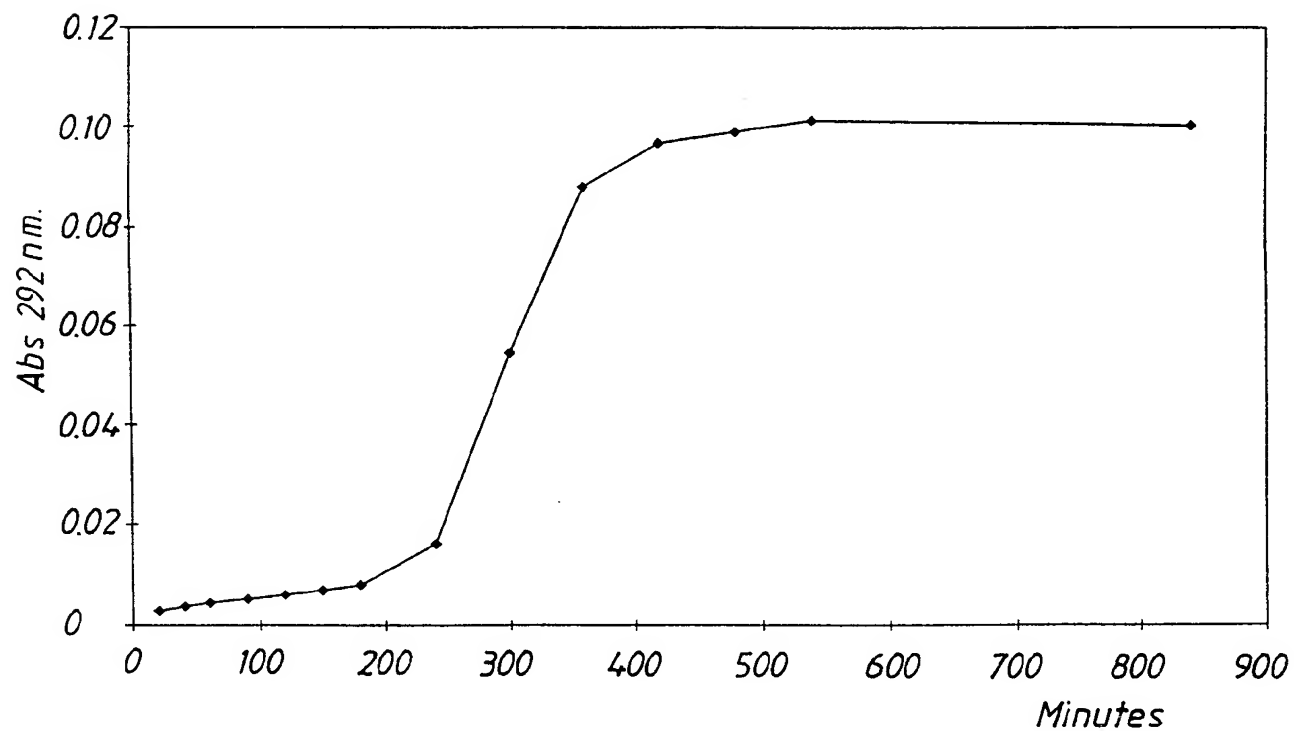
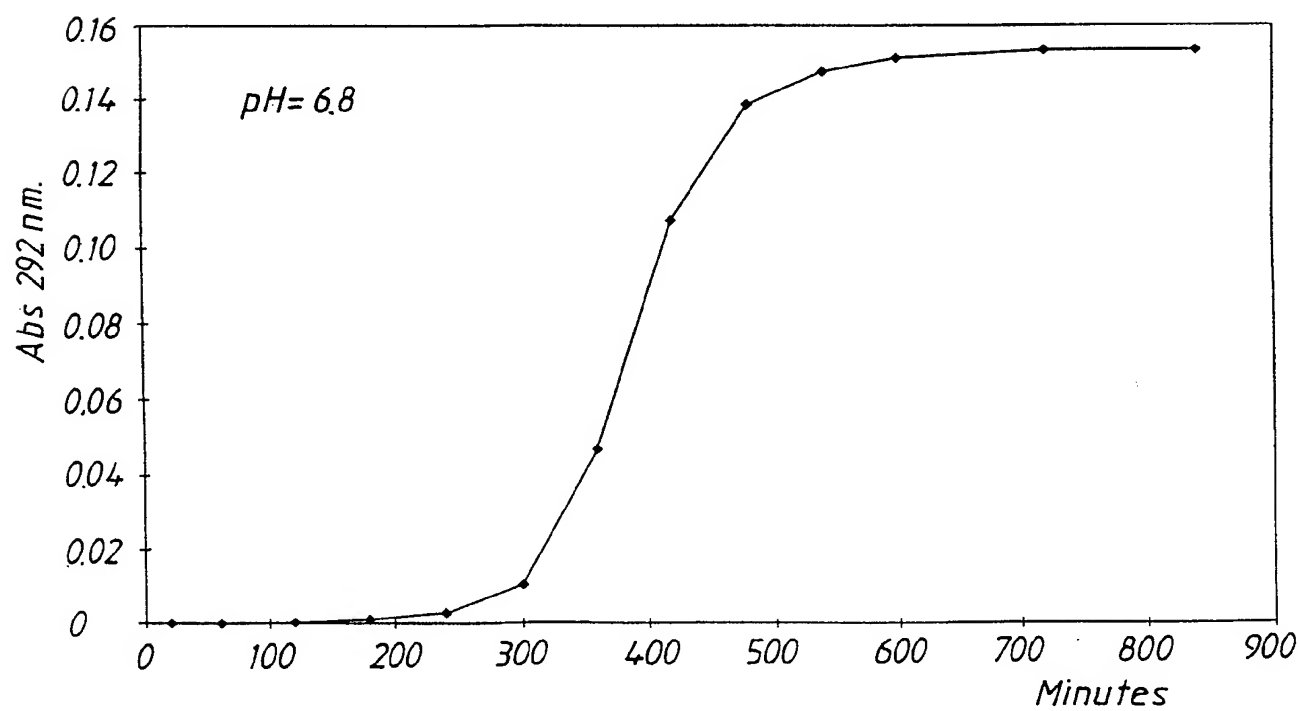
Fig. 2

Fig. 3

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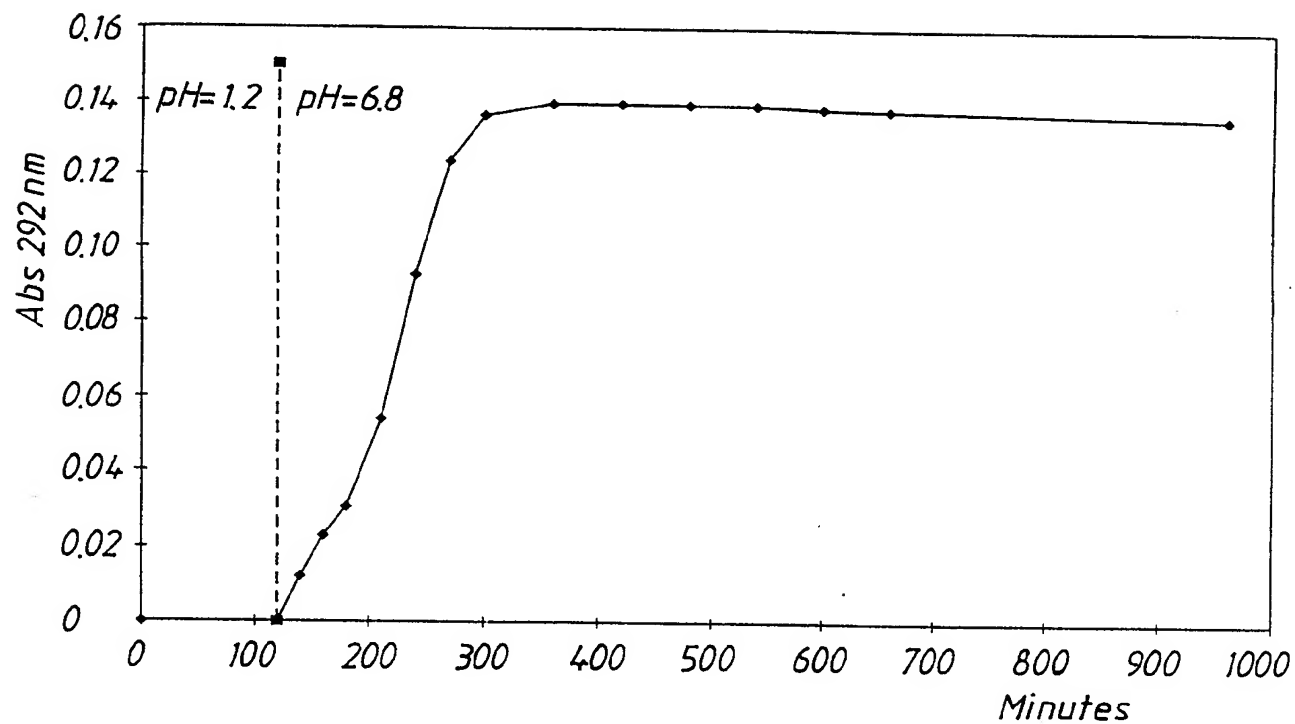
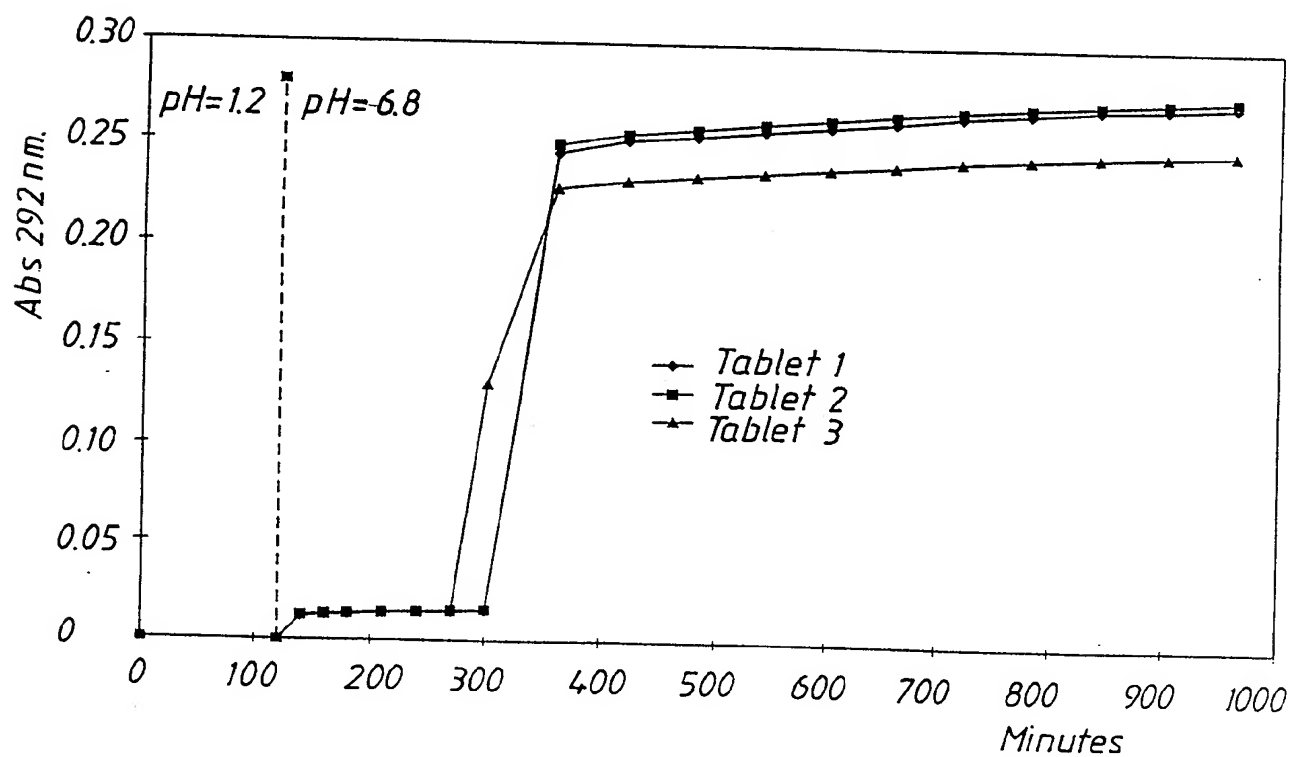
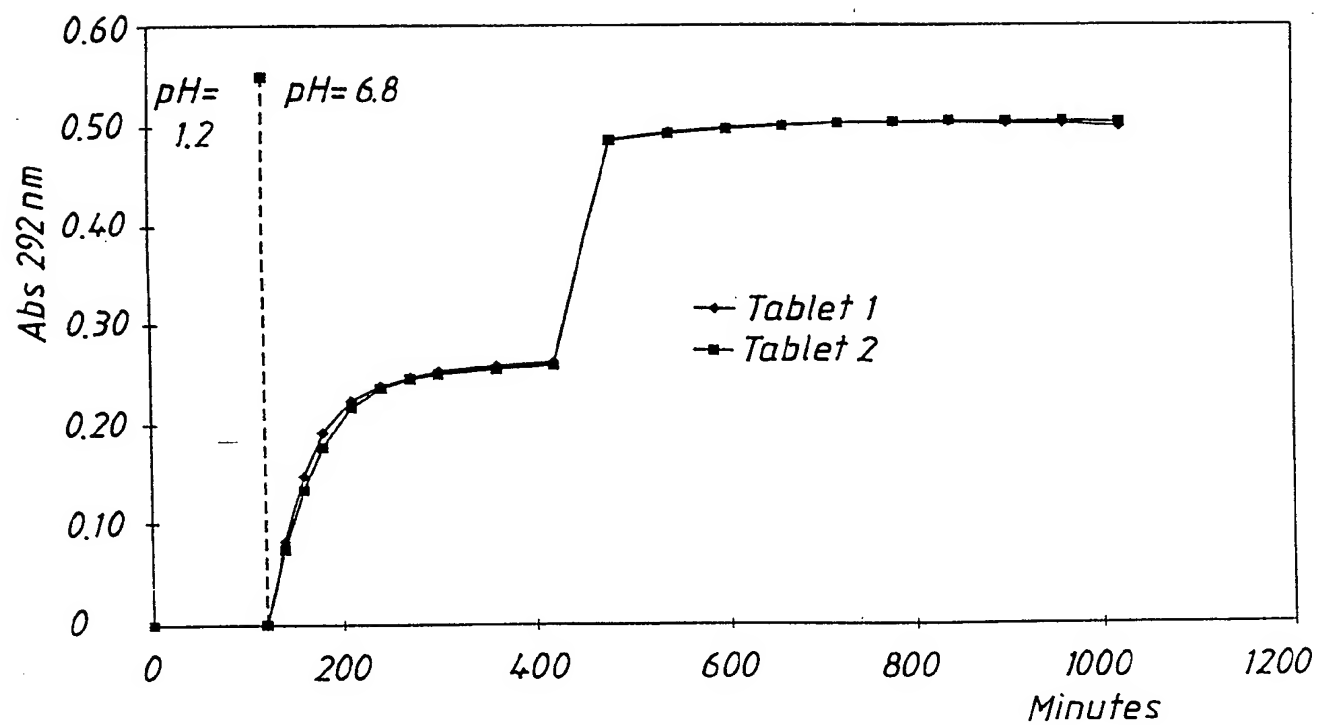


Fig. 4



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Fig. 5



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/02369

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/26, A61K 9/54, A61K 31/44, A61K 31/41
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, TXTE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9702020 A1 (BYK GULDEN LOMBERG CHEMISCHE FABRIK), 23 January 1997 (23.01.97) --	1-29
A	US 5229131 A (GORDON L. AMIDON ET AL), 20 July 1993 (20.07.93), See especially the claims --	7-10,17
A	WO 9601623 A1 (ASTRA AKTIEBOLAG), 25 January 1996 (25.01.96) -- -----	2-3,19

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

13 April 1999

Date of mailing of the international search report

19 -04- 1999

Name and mailing address of the ISA:

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 98/02369

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 28-29

because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Claims 28-29 are directed to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/ compositions.

2. ☐ Claims Nos.:

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/03/99

International application No.

PCT/SE 98/02369

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
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				CA	2232450 A	23/01/97
				EP	0841903 A	20/05/98

US	5229131	A	20/07/93	NONE		

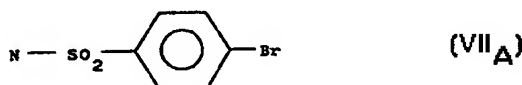
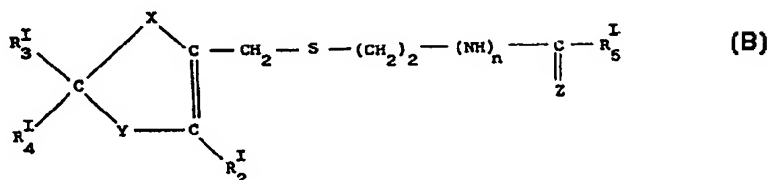
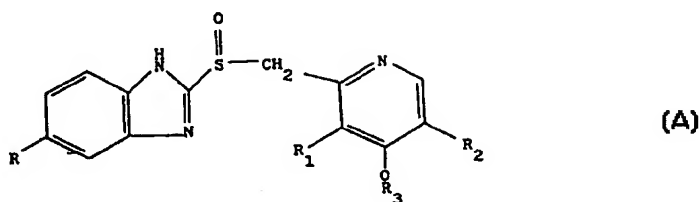
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				SK	30196 A	10/09/97
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				ZA	9505548 A	08/01/96
				SE	9402432 D	00/00/00



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 401/12, 233/61, 307/52, 277/28, 277/48, A61K 31/44, 31/415, 31/34, 31/425	A1	(11) International Publication Number: WO 99/45004 (43) International Publication Date: 10 September 1999 (10.09.99)
(21) International Application Number: PCT/EP99/01226 (22) International Filing Date: 25 February 1999 (25.02.99) (30) Priority Data: MI98A000442 5 March 1998 (05.03.98) IT (71) Applicant (for all designated States except US): NICOX S.A. [FR/FR]; 45, avenue Kléber, F-75116 Paris (FR). (72) Inventor; and (75) Inventor/Applicant (for US only): DEL SOLDATO, Piero [IT/IT]; Via Toti, 22, I-20052 Monza (IT). (74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni, 2, I-20129 Milano (IT).		(81) Designated States: AL, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KP, KR, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>

(54) Title: NITRATE SALT OF ANTI-ULCER MEDICINE



(57) Abstract

Nitrate salt compositions with anti-ulcer medicines having formula (A) and (B) wherein the (A) class compounds: R = H, OCH₃, OCHF₂; R₁ = CH₃, OCH₃; R₂ = H, CH₃; R₃ = CH₃, CH₂-CF₃, (CH₂)₃-OCH₃; wherein the (B) class compounds: R^I₃, R^I₄ equal to or different from each other, are respectively free valence hydrogen, (1), -CH₂-N(CH₃)₂; Y = S, N-R^I₆, CR^I₇R^I₈; X = O, S, N-R^I₁; R^I₂ = H, CH₃; n = 0, 1; Z = N-CN, N-SO₂NH₂, CH-NO₂ or formula (VIIA) R^I₅ = H, -NH-CH₃, NH₂; R^I₆, R^I₇, R^I₈, R^I₁, equal to or different from each other, are hydrogen, free valence. The invention also comprises the methods for the preparation of above salts.

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"NITRATE SALT OF ANTI-ULCER MEDICINE"

* * * * *

The present invention relates to compositions to be used in the therapy and in the prevention of the ulcer relapses and, in general, of dyspepsias. More particularly it relates to compositions having an improved gastroprotective activity combined with a high acid secretion inhibition activity.

Products known in the art and those commercialized and used in the ulcer therapy are compounds which perform an anti-secretory activity (acid secretion inhibition). See for instance " New Guide to Medicine & Drugs" Brit. Medical Assoc. Editor, 1997, pagg. 108-109. Known products having higher therapeutic efficacy show a high anti-secretory activity and are used, both in the acute and in long-term (six months and more) therapies. The drawback of these products is that they have a poor gastroprotective activity, when present. From a practical point of view this means that the gastric protection is not optimal and causes inconveniences above all in the long-term therapy. In this case the presence of frequent relapses due to the enfeeblement of gastric mucosa is noticed.

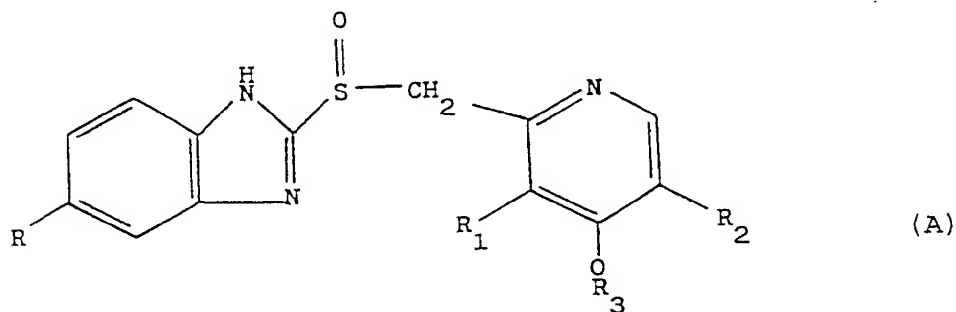
To overcome these inconveniences it is known in the art to add to above medicines other anti-ulcer medicines having a gastroprotective action: prostaglandins, bismuth salts (e.g.

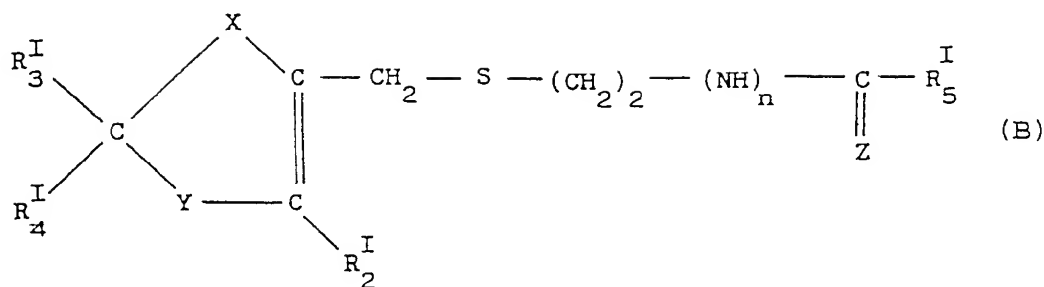
bismuth citrate) and antibiotics. In such way the remission of ulcerous pathology is achieved. However above combinations are not satisfactory as for their tolerability in general. For example it is well known that prostaglandins produce side effects (diarrhoea) towards the intestinal tract; bismuth salts frequently produce nausea and gastric burning. Antibiotics produce unwanted gastrointestinal effects.

The need was felt to have available compositions active in the ulcer and gastric dyspepsia treatment, having improved therapeutic characteristic and tolerability, general and local, in particular having an improved gastroprotective activity combined to a high anti-secretion activity.

The Applicant has unexpectedly and surprisingly found pharmaceutical anti-ulcer compositions having the above mentioned desired properties.

It is an object of the present invention pharmaceutical compositions comprising as essential components nitrate salts of one or more components selected from the following classes of compounds:





where in the (A) class compounds:

$R = H, OCH_3, OCHF_2;$

$R_1 = CH_3, OCH_3;$

$R_2 = H, CH_3;$

$R_3 = CH_3, CH_2-CF_3, (CH_2)_3-OCH_3;$

where in the class (B) compounds:

R_3^I, R_4^I equal to or different from each other, are respectively free valence, hydrogen $-N \equiv C(NH_2)_2$, $-CH_2-N(CH_3)_2$;

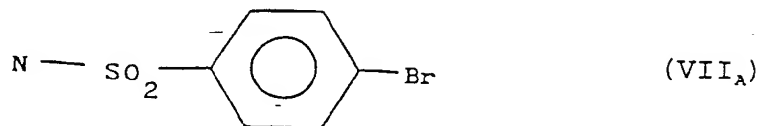
$Y = S, N-R_6^I, CR_7^I R_8^I;$

$X = O, S, N-R_1^I;$

$R_2^I = H, CH_3;$

$n = 0, 1;$

$Z = N-CN, N-SO_2NH_2, CH-NO_2$ or



$R_5^I = H, -NH-CH_3, NH_2;$

$R_6^I, R_7^I, R_8^I, R_1^I$, equal to or different from each other, are hydrogen, free valence.

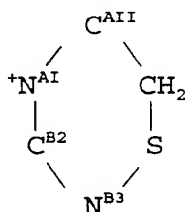
The preferred nitrate salts with the (A) formula precursors are the following:

when $R = OCH_3$, $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$, Omeprazole residue;
as in Omeprazole, but with $R = OCHF_2$, $R_1 = OCH_3$, $R_2 = H$, Pantoprazole residue;

as in Omeprazole, but with $R = H$, $R_2 = H$, $R_3 = (CH_2)_3-OCH_3$, Rabeprazole residue;

as in Rabeprazole, but with $R_3 = CH_2-CF_3$, Lansoprazole residue.

In the (A) class compounds also those having the following intramolecular ring are comprised, obtainable by treating the precursors in an acid aqueous environment (rif. "A Textbook of Drug Design and Development", Harwood Academic Publisher, 1991, pag. 140):



wherein N^{AI} and C^{AII} mean, respectively, the nitrogen and carbon atom in 1 and 2 position of the pyridine ring of formula A and C^{B2} and N^{B3} the carbon and nitrogen atom, respectively, in 2 and 3 position of the imidazole ring (1 position of the imidazole ring is that of the proton nitrogen).

The preferred nitrate salts with the (B) formula precursors are the following:

when in (B) formula $X = N-R^I_1$ with R^I_1 free valence, $Y = N-R^I_6$ with $R^I_6 = H$, $R^I_3 = H$, R^I_4 is a free valence and forms with R^I_1

a double bond, $R^I_2 = CH_3$, $n = 1$, $R^I_5 = -NH-CH_3$, $Z = N-CN$, Cimetidine residue;

when $X = N-R^I_1$ with R^I_1 free valence, $Y = S$,

$R^I_3 = -N=C(NH_2)_2$, R^I_4 is a free valence and forms with R^I_1 a double bond, $R^I_2 = H$, $n = 1$, $R^I_5 = H$, $Z = (VII_A)$, Ebrotidine residue;

as in Ebrotidine but with $n = 0$, $R^I_5 = NH_2$ and $Z = N-SO_2NH_2$, Famotidine residue ;

as in Ebrotidine but with $R^I_3 = -CH_2-N(CH_3)_2$, $R^I_5 = -NH-CH_3$ and $Z = CH-NO_2$, Nizatidine residue;

as in Nizatidine, but with $X = \text{oxygen}$, $Y = CR^I_7R^I_8$ with R^I_7 hydrogen and R^I_8 free valence, R^I_4 is a free valence and forms with R^I_8 a double bond, Ranitidine residue.

In the compositions according to the present invention also isomers of the compounds belonging to (A) and (B) classes may be used.

In the compositions according to the present invention the compound salts of above classes contain at least one mole of nitrate ion/mole of compounds. Preferably the ratio between the nitrate ion moles and the precursor is equal to one. Salts having a higher molar ratio are obtained when in the molecule other amino groups basic enough to be salified are present.

Salt precursors belonging to the above mentioned classes are prepared according to the methods described in "The Merck Index 12^a Ed." (1996), herein completely incorporated by reference.

The salts of the present invention may be prepared accor-

ding to one of the following methods.

When the substance to be salified is available as free base or as a soluble corresponding salt in an organic solvent, which preferably does not contain hydroxyl groups, for example acetonitrile, ethyl acetate, tetrahydrofuran ecc., the salt is prepared by dissolving the substance in the solvent at a concentration preferably equal or higher than 10% w/v, by adding the amount of concentrated nitric acid corresponding to the moles of salifiable aminic groups present in the compound. The nitric acid is preferably diluted in the same solvent. Preferably during and after the addition the mixture is cooled to temperatures in the range 20°-0°C. The product is generally recovered by filtration and washed with the solvent.

When on the contrary the substance is not much soluble or it is available as a not much soluble salt in the above mentioned solvents, the corresponding mixtures with hydroxylated solvents may be used. Examples of such solvents are methyl alcohol, ethyl alcohol and water. The precipitation can be quickened by diluting then the so obtained mixture, after the addition of nitric acid, with an apolar solvent.

When the starting product is salified with hydrochloric acid it is possible to prepare the salt with nitric acid directing adding silver nitrate to the compound solution. After filtering silver chloride, the solution is concentrated and cooled to recover the nitrate salt.

When the starting product is a salt, it is possible to liberate the corresponding base by a treatment with a sodium

or potassium carbonate or bicarbonate saturated solution, or with a sodium or potassium hydroxide diluted solution. The base is then extracted by a suitable organic solvent (e.g. halogenated solvents, esters, ethers) which is then dried. The organic solution is evaporated and then one proceeds according to the preceding preparation methods, by dissolving the base in acetonitrile or in the other above mentioned solvents.

It has now srprisingly been found that the compositions of the present invention allow to improve, compared with the known above mentioned combinations, the comprehensive pharmacotoxicological situation of precursors, increasing the therapeutic efficacy and their general and local tolerability in the ulcer and gastric dyspepsia treatment with an improved gastroprotective activity.

The compositions of the present invention are formulated in the corresponding pharmaceutical compositions according to well known techniques in this field together with the common excipients; see for example the volume "Remington's Pharmaceutical Sciences 15a Ed."

The invention salt dosages are the conventional ones of their precursors of (A) and (B) classes.

It is a further object of the present invention the compositions obtainable combining one or more nitrate salts of the compounds of (A) and (B) classes, or their pharmaceutical compositions, with conventional gastroprotectives. As examples, prostaglandines, bismuth salts, active antibiotics towards pathogenic microorganisms in the gastrointestinal mucosa

can be mentioned. It has surprisingly been found that gastro-protective activity of the invention compositions is very high. This makes it possible to avoid the undesirable effects of known gastroprotectives when they are used in combination with compounds or formulation of the invention. It has indeed been found that the amount of known gastroprotectives, in the combination of the invention, is lower compared with those known and does not cause undesirable effects. The skilled in this field is able to easily determine the maximum amount of conventional gastroprotectives to be combined with the pharmaceutical compositions of the invention since this corresponds to the absence of typical side effects of known gastroprotectives. In any case the amount of conventional gastroprotectives to be used in the combination is lower than that used in the combinations described in the art.

The following examples have the purpose to illustrate the invention and must not be considered as limitative of the same.

EXAMPLE 1

Preparation of cimetidine nitrate salt.

10 g of cimetidine are dissolved in 100 ml of an acetonitrile/tetrahydrofuran/water 1 : 1 : 2 (composition by volume) mixture cooled at +4°C. 10 ml acetonitrile solution containing 2.5 ml of 70% nitric acid are added little by little. The solution is diluted with ethyl ether, maintaining the temperature at +4°C, till to incipient precipitation of the product.

After a some hour rest the precipitated solid is filtered, washed with ethyl ether and dried. 12.1 g of cimetidine mononitrate salt are recovered having m.p. 158°-159°C (with decomposition).

¹H-NMR (D₂O): 8,55 (1H, s), 3,83 (2H, s), 3,32 (2H, s), 2,77 (3H, s), 2,68 (2H, t), 2,32 (3H, s).

Elementary analysis:

calc. (%)	C 38,09	H 5,43	N 31,09	S 10,17
found (%)	C 37,99	H 5,41	N 31,16	S 10,25

EXAMPLE 2

Preparation of ranitidine nitrate salt.

5 g of ranitidine hydrochloride are dissolved in a 140 ml acetonitrile/methyl alcohol 6 : 1 mixture at + 20°C. 4,2 g of powder silver nitrate are added. The silver chloride precipitate is filtered, the precipitate is washed with an acetonitrile/methyl alcohol 6 : 1 solution, the organic phases are put together, dried and treated to obtain a dry residue. 3,5 g of an amorphous solid corresponding to the ranitidine mononitrate salt are obtained.

¹H-NMR (D₂O) : 6,70 (1H, d), 6,40 (1H, d), 4,34 (2H, s), 3,83 (2H, s), 3,43 (2H, t), 2,93 (2H, m), 2,87 (9H, s).

calc. (%)	C 41,37	H 6,14	N 18,56	S 8,50
found (%)	C 41,12	H 6,20	N 18,44	S 8,38

PHARMACOLOGICAL TESTS

EXAMPLE 3

Acute Toxicity

A single dose equal to 100 mg/Kg respectively of cimetidine

dine and ranitidine nitrate salts, dealt with in the previous Examples, has been given to a group of 10 rats weighing 20 g each by a cannula by oral way in a carboxymethylcellulose aqueous suspension 2% w/v.

The animals are kept under observation for 14 days. In no one of the group animals the toxic symptom presence was noted.

EXAMPLE 4

Anti-ulcer Activity

Anti-ulcer activity is evaluated according to the experimental model described in the paper of A. Robert e Al.

"Cytoprotection by prostaglandins in rats. Prevention of gastric necrosis produced by alcohol, HCl, NaOH, hypertonic NaCl and thermal injury" Gastroenterology 77, 433-43 1979.

To 5 groups of 10 rats each, kept on empty stomach since the previous night, 15 minutes before the supply of absolute ethyl alcohol (1 ml), by oral way are supplied:

- 5 ml/Kg of carboxymethylcellulose aqueous suspension 2%.
- 50 mg/Kg of cimetidine in 5 ml/Kg of carboxymethylcellulose aqueous suspension 2%.
- 62,5 mg/Kg of cimetidine nitrate (corresponding to 50 mg/Kg of cimetidine) in 5 ml/Kg of carboxymethylcellulose aqueous suspension 2%.
- 50 mg/Kg of ranitidine in 5 ml/Kg of carboxymethylcellulose aqueous suspension 2%.
- 60 mg/Kg of ranitidine nitrate (corresponding to 60 mg/Kg of ranitidine) in 5 ml/Kg of carboxymethylcellulose aqueous suspension 2%.

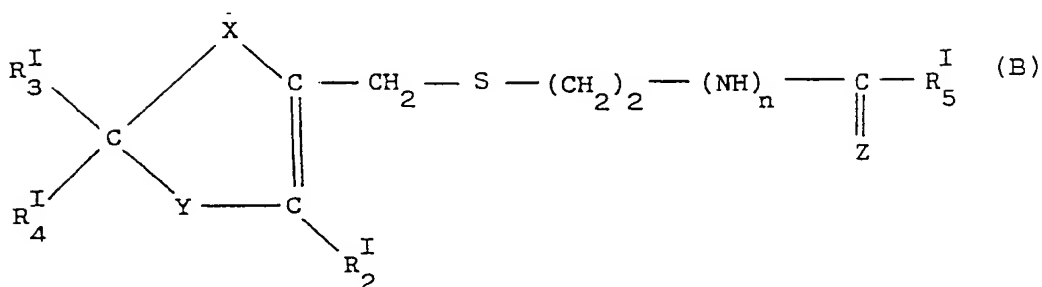
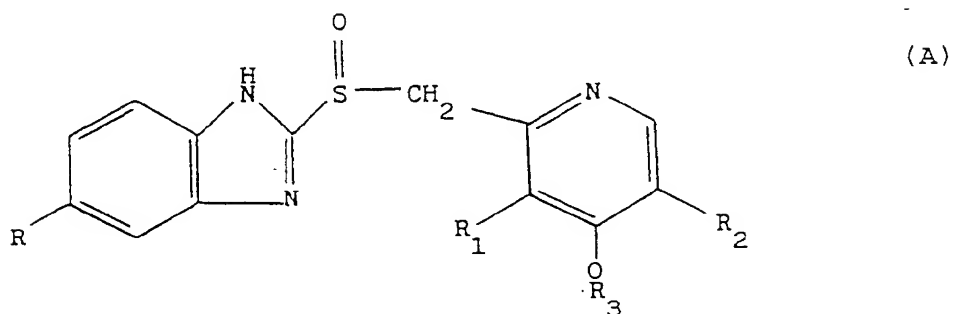
A hour later the animals are sacrificed and the gastric lesion incidence is evaluated. Results are reported in Table 1 and they show that cimetidine and ranitidine nitrate salts have an improved gastroprotective activity compared with the corresponding starting products.

TABLE I

Treatment	Gastric Damage (%)
Vehicle	100
Cimetidine	100
Cimetidine.HNO ₃	50
Ranitidine	80
Ranitidine.HNO ₃	40

CLAIMS

1. Nitrate salts of one or more components selected from the following compound classes:



where in the (A) class compounds:

$R = H, OCH_3, OCHF_2;$

$R_1 = CH_3, OCH_3;$

$R_2 = H, CH_3;$

$R_3 = CH_3, CH_2-CF_3, (CH_2)_3-OCH_3;$

where in the (B) class compounds:

R_3^I, R_4^I equal to or different from each other, are respectively free valence, hydrogen, $-N=C(NH_2)_2$,

$-CH_2-N(CH_3)_2;$

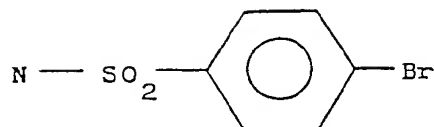
$Y = S, N-R_6^I, CR_7^I, R_8^I;$

$X = O, S, N-R^I_1;$

$R_2 = H, CH_3;$

$n = 0, 1;$

$Z = N-CN, N-SO_2NH_2, CH-NO_2$ or

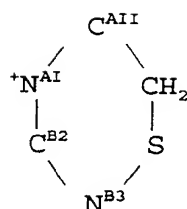


(VII_A)

$R^I_5 = H, -NH-CH_3, NH_2;$

$R^I_6, R^I_7, R^I_8, R^I_1$, equal or different from each other, are hydrogen, free valence.

2. Salts according to claim 1 where in the compounds of (A) formula $R = OCH_3$, $R_1 = CH_3$, $R_2 = CH_3$, $R_3 = CH_3$, Omeprazole residue;
as in Omeprazole, but with $R = OCHF_2$, $R_1 = OCH_3$, $R_2 = H$,
Pantoprazole residue;
as in Omeprazole, but with $R = H$, $R_2 = H$, $R_3 = (CH_2)_3-OCH_3$,
Rabeprazole residue;
as in Rabeprazole, but with $R_3 = CH_2-CF_3$, Lansoprazole residue.
3. Salts according to claims 1 e 2 comprising (A) formula compounds having the following intramolecular ring, obtainable by treating the precursors in acid environment:



wherein N^{AI} e C^{AII} are, respectively, the nitrogen and carbon atom in 1 and 2 position of the pyridine ring and C^{B2} and N^{B3} the carbon and nitrogen atom, respectively, in 2 and 3 position of the imidazole ring.

4. Salts according to claim 1 where in (B) formula $X = N-R^I_1$ with R^I_1 free valence, $Y = N-R^I_6$ with $R^I_6 = H$, $R^I_3 = H$, R^I_4 is a free valence and forms with R^I_1 a double bond, $R^I_2 = CH_3$, $n = 1$, $R^I_5 = -NH-CH_3$, $Z = N-CN$, Cimetidine residue;

when in (B) formula $X = N-R^I_1$ with R^I_1 free valence, $Y = S$, $R^I_3 = -N=C(NH_2)_2$, R^I_4 is a free valence and forms with R^I_1 a double bond, $R^I_2 = H$, $n = 1$, $R^I_5 = H$, $Z = (VII_A)$, Ebrotidine residue;

as in Ebrotidine but with $n = 0$, $R^I_5 = NH_2$ and $Z = N-SO_2-NH_2$, Famotidine residue;

as in Ebrotidine but with $R^I_3 = -CH_2-N(CH_3)_2$, $R^I_5 = -NH-CH_3$ and $Z = CH-NO_2$, Nizatidine residue;

as in Nizatidine, but with $X = \text{oxygen}$, $Y = CR^I_7R^I_8$ with R^I_7 hydrogen and R^I_8 free valence, R^I_4 is a free valence and forms with R^I_1 a double bond, Ranitidine residue.

5. Nitrate salts according to claims 1-4, containing one or more isomers of the compounds belonging to (A) and (B)

classes.

6. Salts according to claims 1-5, wherein the compound salts of (A) and (B) classes contain at least one mole of nitrate ion/mole of compound.
7. Pharmaceutical compositions of nitrate salts according to claims 1-6.
8. Nitrate salts and pharmaceutical compositions according to claims 1-7 for use as medicament.
9. Use of the salt and composition according to claim 8 for the preparation of medicaments for the treatment of ulcers and gastric dyspepsias.
10. Use according to claims 8-9 wherein the salt and pharmaceutical composition dosages are the conventional ones of their (A) and (B) class precursors.
11. Compositions obtainable by combining one or more nitrate salts of (A) and (B) class compounds, or their pharmaceutical compositions, according to claims 1-10 with conventional gastroprotectives .
12. Compositions according to claim 11 wherein conventional gastroprotectives are selected from prostaglandins, bismuth salts and antibiotics.
13. Use of compositions according to claims 11-12 for preparing medicines for the therapy and prevention of ulcer and dyspepsia relapses.
14. Preparation process of nitrate salts according to claims from 1 to 6 wherein, when the substance to be salified is available as free base or as a soluble corresponding salt

in an organic solvent which does not contain hydroxyl groups the salt is prepared by dissolving the substance in the solvent at a concentration equal or higher than 10% w/v, by adding the amount of concentrated nitric acid corresponding to the moles of salifiable aminic groups present in the compound, by cooling during and after the addition at temperatures in the range 20°-0°C and by recovering the product by filtration.

15. Process according to claim 14 wherein when the substance is not much soluble or it is available as a not much soluble salt in the above mentioned solvent, the corresponding mixtures with hydroxylated solvents are used and the precipitation is quickened by diluting the so obtained mixture, after the addition of nitric acid, with an apolar solvent.
16. Process according to claims 14-15 wherein when the starting material is salified with hydrochloric acid, the salt with nitric acid is prepared by directly adding silver nitrate to the compound solution, by filtering the silver chloride; the solution is then concentrated and cooled to recover the nitric salt.
17. Process for the preparation of nitrate salts according to claims from 1 to 6 wherein when the starting product is a salt, the corresponding base is liberated by a treatment with a sodium or potassium carbonate or bicarbonate saturated solution or with a sodium or potassium hydroxide diluted solution, by extracting the

base with a suitable organic solvent and by following the methods to prepare the nitrate salt mentioned at the claims 14 or 15.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/01226

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D401/12 C07D233/61 C07D307/52 C07D277/28 C07D277/48
A61K31/44 A61K31/415 A61K31/34 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 285 681 A (HEUMANN PHARMA GMBH & CO) 12 October 1988 see page 5, line 33 - line 38; claims ---	1,4-17
X	DE 23 44 779 A (SMITH KLINE FRENCH LAB) 14 March 1974 see page 3; claims ---	1,4-17
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

1 June 1999

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INTERNATIONAL SEARCH REPORT

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PCT

特許協力条約に基づいて公開された国際出願

<p>(51) 国際特許分類6 A61K 31/44, 9/28, 47/02, 47/32, 47/38</p>	<p>A1</p>	<p>(11) 国際公開番号 WO99/53918</p> <p>(43) 国際公開日 1999年10月28日 (28.10.99)</p>		
<table border="1"> <tr> <td data-bbox="131 417 833 1087"> <p>(21) 国際出願番号 PCT/JP99/02098</p> <p>(22) 国際出願日 1999年4月20日 (20.04.99)</p> <p>(30) 優先権データ 特願平10/109288 1998年4月20日 (20.04.98)</p> <p>(71) 出願人 (米国を除くすべての指定国について) エーザイ株式会社(EISAI CO., LTD.)[JP/JP] 〒112-8088 東京都文京区小石川4丁目6番10号 Tokyo, (JP)</p> <p>(72) 発明者 ; および</p> <p>(75) 発明者 / 出願人 (米国についてののみ) 鶴飼宏治(UKAI, Koji)[JP/JP] 〒500-8384 岐阜県岐阜市藪田南3-3-1 STEP井上203 Gifu, (JP) 市川正己(ICHIKAWA, Masaki)[JP/JP] 〒300-0065 茨城県土浦市常名4016-129 Ibaraki, (JP) 加藤 隆(KATO, Takashi)[JP/JP] 〒305-0031 茨城県つくば市吾妻3-16-2 セラヴィ203 Ibaraki, (JP) 菅谷幸子(SUGAYA, Yukiko)[JP/JP] 〒305-0035 茨城県つくば市松代3-305-302 Ibaraki, (JP) 鈴木康之(SUZUKI, Yasuyuki)[JP/JP] 〒305-0854 茨城県つくば市上横場2520-4 Ibaraki, (JP)</p> </td> <td data-bbox="833 417 1528 1087"> <p>青木 茂(AOKI, Shigeru)[JP/JP] 〒501-6027 岐阜県羽島郡川島町緑町2-15 Gifu, (JP) 加藤晃良(KATO, Akira)[JP/JP] 〒305-0035 茨城県つくば市松代5-2-27 Ibaraki, (JP) 河村政男(KAWAMURA, Masao)[JP/JP] 〒367-0063 埼玉県本庄市下野堂67-13 Saitama, (JP) 藤岡 賢(FUJIOKA, Satoshi)[JP/JP] 〒491-0051 愛知県一宮市今伊勢町馬寄字舟入39番地の1 Aichi, (JP)</p> <p>(74) 代理人 弁理士 古谷 馨, 外(FURUYA, Kaoru et al.) 〒103-0012 東京都中央区日本橋堀留町1-8-11 日本橋TMビル Tokyo, (JP)</p> <p>(81) 指定国 CA, CN, KR, US, 欧州特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE)</p> <p>添付公開書類 国際調査報告書</p> </td> </tr> </table>			<p>(21) 国際出願番号 PCT/JP99/02098</p> <p>(22) 国際出願日 1999年4月20日 (20.04.99)</p> <p>(30) 優先権データ 特願平10/109288 1998年4月20日 (20.04.98)</p> <p>(71) 出願人 (米国を除くすべての指定国について) エーザイ株式会社(EISAI CO., LTD.)[JP/JP] 〒112-8088 東京都文京区小石川4丁目6番10号 Tokyo, (JP)</p> <p>(72) 発明者 ; および</p> <p>(75) 発明者 / 出願人 (米国についてののみ) 鶴飼宏治(UKAI, Koji)[JP/JP] 〒500-8384 岐阜県岐阜市藪田南3-3-1 STEP井上203 Gifu, (JP) 市川正己(ICHIKAWA, Masaki)[JP/JP] 〒300-0065 茨城県土浦市常名4016-129 Ibaraki, (JP) 加藤 隆(KATO, Takashi)[JP/JP] 〒305-0031 茨城県つくば市吾妻3-16-2 セラヴィ203 Ibaraki, (JP) 菅谷幸子(SUGAYA, Yukiko)[JP/JP] 〒305-0035 茨城県つくば市松代3-305-302 Ibaraki, (JP) 鈴木康之(SUZUKI, Yasuyuki)[JP/JP] 〒305-0854 茨城県つくば市上横場2520-4 Ibaraki, (JP)</p>	<p>青木 茂(AOKI, Shigeru)[JP/JP] 〒501-6027 岐阜県羽島郡川島町緑町2-15 Gifu, (JP) 加藤晃良(KATO, Akira)[JP/JP] 〒305-0035 茨城県つくば市松代5-2-27 Ibaraki, (JP) 河村政男(KAWAMURA, Masao)[JP/JP] 〒367-0063 埼玉県本庄市下野堂67-13 Saitama, (JP) 藤岡 賢(FUJIOKA, Satoshi)[JP/JP] 〒491-0051 愛知県一宮市今伊勢町馬寄字舟入39番地の1 Aichi, (JP)</p> <p>(74) 代理人 弁理士 古谷 馨, 外(FURUYA, Kaoru et al.) 〒103-0012 東京都中央区日本橋堀留町1-8-11 日本橋TMビル Tokyo, (JP)</p> <p>(81) 指定国 CA, CN, KR, US, 欧州特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE)</p> <p>添付公開書類 国際調査報告書</p>
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<p>(54)Title: STABILIZED COMPOSITIONS CONTAINING BENZIMIDAZOLE-TYPE COMPOUNDS</p> <p>(54)発明の名称 安定化したベンズイミダゾール系化合物含有組成物</p> <p>(57) Abstract Chemically stabilized preparations of benzimidazole-type compounds. These compositions comprise the benzimidazole-type compounds or alkali metal salts thereof together with at least one substance selected from among sodium carbonate, potassium carbonate, sodium hydroxide, potassium hydroxide, aminoalkyl methacrylate copolymer E, arginine aspartate, hydroxypropyl cellulose and crospovidone.</p>				

(57)要約

本発明は、ベンズイミダゾール系化合物の化学的に安定な製剤を提供する。すなわち、ベンズイミダゾール系化合物又はそのアルカリ金属塩に炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム、アミノアルキルメタアクリレートコポリマーE、アルギニンアスパラギン酸塩、ヒドロキシプロピルセルロース及びクロスボビドンから選ばれる1種以上の物質を配合してなる組成物である。

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明細書

安定化したベンズイミダゾール系化合物含有組成物

発明の属する技術分野

本発明は、ベンズイミダゾール系化合物又はそのアルカリ金属塩を含有する内服固形製剤に関する。

従来技術

ベンズイミダゾール系化合物又はそのアルカリ金属塩は、いわゆるプロトンポンプの強い阻害作用を有し、胃酸分泌を抑制することにより、胃潰瘍、十二指腸潰瘍等の治療剤として広く使用されている。一方、ベンズイミダゾール系化合物は化学的に非常に不安定なため、製剤化にあたっては種々の工夫がなされている。例えば、特開昭62-277322号公報にはベンズイミダゾール系化合物にマグネシウム及び／又はカルシウムの塩基性無機塩を配合することを特徴とする安定化された医薬組成物の製法が開示され、特開昭62-258320号公報にはベンズイミダゾール系化合物を含む核部分にアルカリ化合物を配合し、水溶性ないし水で急速に分解する錠剤の賦形剤、又は重合体で水溶性のフィルム形成化合物等により被覆しさらに腸溶性皮膜で被覆する経口医薬製剤が開示されている。

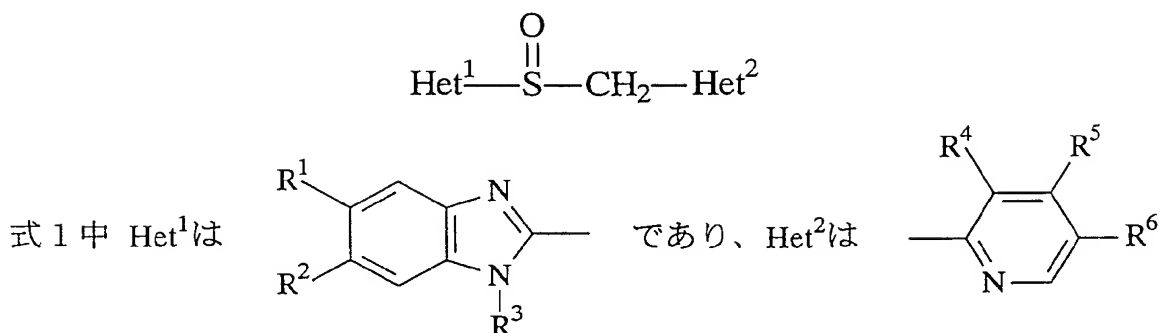
しかしながら、上記技術によっても製剤における安定性は充分ではなく、更なる改善が求められている。すなわち本発明は、ベンズイミダゾール系化合物を含有する内服固形製剤のより一層の安定化を目的とするものである。

発明の開示

本発明は、下記に示す構造式（式1）で示されるベンズイミダゾール系化合物又はそのアルカリ金属塩に炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム、アミノアルキルメタアクリレートコポリマーE、アルギニンアスパラギン酸塩、ヒドロキシプロピルセルロース及びクロスポビドンから選ばれる

1 種以上の物質を配合してなる組成物である。

式 1



であり、R¹およびR²は同じかまたは異なっていて、水素、メトキシ及びジフルオロメトキシから選択され、R³は水素及びナトリウムから選択され、R⁴、R⁵およびR⁶は同じかまたは異なっていて、水素、メチル、メトキシ、メトキシプロポキシ及びトリフルオロエトキシから選択される。

さらに、本発明は式 1 で示されるベンズイミダゾール系化合物又はそのアルカリ金属塩に炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム、アミノアルキルメタアクリレートコポリマーE、アルギニンアスパラギン酸塩、ヒドロキシプロピルセルロース及びクロスボビドンから選ばれる 1 種以上の物質を配合してなる核に腸溶性皮膜を被覆した製剤である。

また、本発明は式 1 で示されるベンズイミダゾール系化合物又はそのアルカリ金属塩に炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム、アミノアルキルメタアクリレートコポリマーE、アルギニンアスパラギン酸塩、ヒドロキシプロピルセルロース及びクロスボビドンから選ばれる 1 種以上の物質を配合してなる核に中間皮膜を被覆し、更に腸溶性皮膜を被覆した製剤である。

本発明は、また、式 1 で示されるベンズイミダゾール系化合物又はそのアルカリ金属塩に、炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム、アミノアルキルメタアクリレートコポリマーE、アルギニンアスパラギン酸塩、ヒドロキシプロピルセルロース及びクロスボビドンから選ばれる 1 種以上の物質を配合してなる核に中間皮膜を被覆し、更に腸溶性皮膜を被覆し、次に防湿性皮膜を被覆した製剤である。

本発明は、(A) 式 1 で示されるベンズイミダゾール系化合物又はそのアルカリ金属塩および (B) 炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム、アミノアルキルメタアクリレートコポリマーE、アルギニンアスパラギン酸塩、ヒドロキシプロピルセルロース及びクロスポビドンからなる群より選ばれる少なくとも 1 種の物質を含む医薬組成物である。

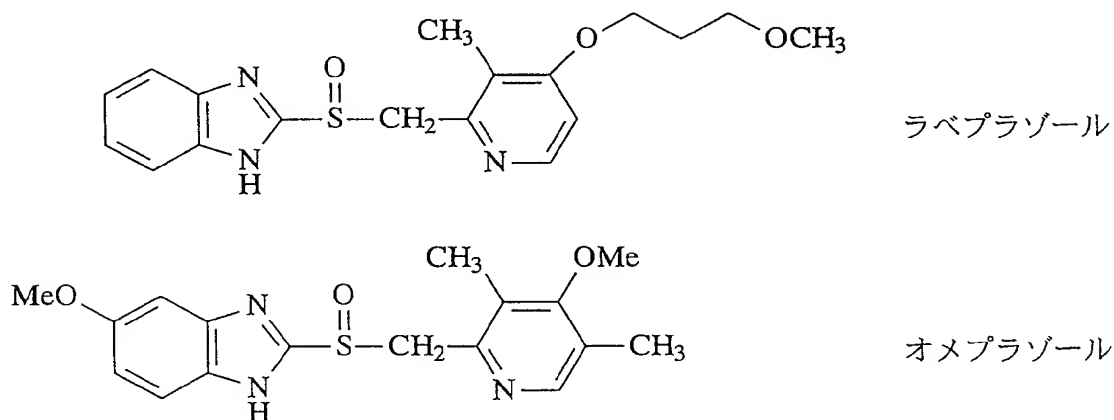
また本発明は、上記の組成物よりなる核および腸溶性皮膜よりなる医薬製剤である。製剤は核の他に、中間皮膜、腸溶性皮膜及び防湿性皮膜を含んでもよい。

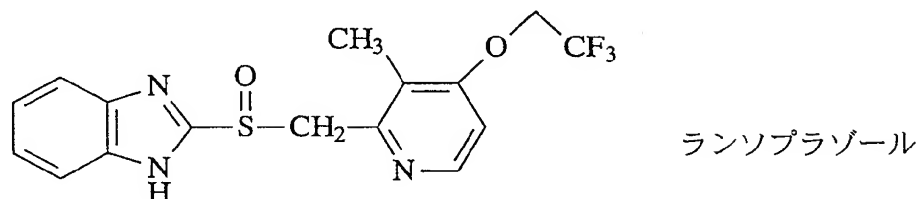
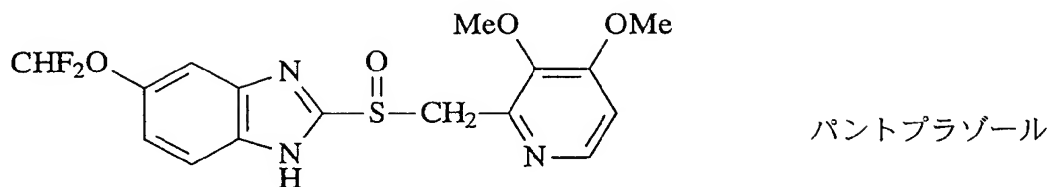
防湿性皮膜は、ベンズイミダゾール系化合物にとどまらず、水分存在下で分解が促進され、且つ胃酸との接触時にも分解促進が認められる薬物にも有用である。即ち、本発明は、水分存在下で分解が促進され且つ胃酸中で化学的に不安定な薬物を配合してなる核に腸溶性皮膜を被覆し、更に防湿性皮膜を被覆した製剤である。

また、本発明は、水分存在下で分解が促進され且つ胃酸中で化学的に不安定な薬物を配合してなる核に中間皮膜を被覆し、更に腸溶性皮膜を被覆し、次に防湿性皮膜を被覆した製剤である。

本発明におけるベンズイミダゾール系化合物又はそのアルカリ金属塩の好ましい例としては、ラベプラゾール、オメプラゾール、パントプラゾール、ランソプラゾールまたはそのナトリウム塩、カリウム塩等を挙げることができる。各化合物の構造式を式 3 に示す。

式 3





以下、ベンズイミダゾール系化合物又はそのアルカリ金属塩をベンズイミダゾール系化合物と称する。

本発明におけるベンズイミダゾール系化合物は公知の方法により製造することができる。例えば、特開昭52-62275号公報、特開昭54-141783号公報、特開平1-6270号公報等の開示される方法により製造することができる。

本発明における炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム及びヒドロキシプロピルセルロースは日本薬局方収載品であり、市販のものを容易に入手できる。アミノアルキルメタアクリレートコポリマーEは日本薬局方外医薬品規格に収載されており、容易に入手可能である。また、クロスボビドンは医薬品添加物規格に収載されている物質であり、粒径の異なる種々のグレードの市販品を容易に入手可能であるが、必要に応じてハンマーミル等の粉碎装置を用いて粒径を調整できる。

本発明におけるベンズイミダゾール系化合物と炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム、アミノアルキルメタアクリレートコポリマーE、アルギニンアスパラギン酸塩、ヒドロキシプロピルセルロース及びクロスボビドンから選ばれる1種以上の物質との配合比率は、ベンズイミダゾール系化合物1重量部に対して総量で0.01~20重量部、好ましくは0.01~10重量部、さらに好ましくは0.1~10重量部である。本発明においては、炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム、アミノアルキル

メタアクリレートコポリマーE、アルギニンアスパラギン酸塩、ヒドロキシプロピルセルロース及びクロスポビドンを単独で用いることもできるし、またこれらを2種以上組み合わせて用いることもできる。これらのうち、ベンズイミダゾール系化合物に水酸化ナトリウム、水酸化カリウム及び/又は炭酸ナトリウムを配合することが効果的であり、ベンズイミダゾール系化合物に1) クロスポビドンと2) 水酸化ナトリウム、水酸化カリウム及び/又は炭酸ナトリウムを配合すると更に効果的である。この物質の組み合わせにおいて、配合比率は、ベンズイミダゾール系化合物1重量部に対して0.01～20重量部であるが、望ましくは、クロスポビドンが0.5～5重量部、水酸化ナトリウム、水酸化カリウム及び/又は炭酸ナトリウムが0.01～2重量部である。

ベンズイミダゾール系化合物は、加温・加湿保存条件下における分解時には、特に色の着色変化が大きく認められる。本発明における上記の種々の添加剤を配合した組成物及び/又は製剤は、含量安定性の向上だけでなく、着色変化を抑制するという極めて顕著な効果を有している。

本発明に係るベンズイミダゾール系化合物と炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム、アミノアルキルメタアクリレートコポリマーE、アルギニンアスパラギン酸塩、ヒドロキシプロピルセルロース及びクロスポビドンから選ばれる1種以上の物質を配合してなる組成物を用いて製剤を製造するには、通常用いられる乳糖、マンニトール等の賦形剤を用いることができる。結合剤としてはヒドロキシプロピルセルロース、崩壊剤としてはクロスポビドンを用いることが望ましい。

また、一般に崩壊剤として用いられるクロスポビドンは、微粉碎することにより本来の崩壊剤としての崩壊力、膨潤力を減少させる事ができることが知られている。微粉碎化した粒径の小さいクロスポビドンは、本発明においてはベンズイミダゾール系化合物の安定化剤として使用するものであり、通常の崩壊剤としての添加量（通常は10%以下）を上回る添加が可能である。微粉碎化したクロスポビドンの平均粒径は、数 μm ～50 μm 、4 μm ～50 μm がさらに望ましい。

したがって、本発明に係る組成物又は製剤において、クロスポビドンは、平均

粒径が数 μm ～50 μm 、好ましくは4 μm ～50 μm の粒径の小さい微粉クロスボビドンを使用することが好ましい。もちろん、微粉クロスボビドンと通常のクロスボビドンを併用してもよい。

また、クロスボビドン中には、製造メーカーやロットにより異なるものの、不純物として極微量の過酸化物を含有していることが多い。ベンズイミダゾール系化合物は酸化されやすい性質を有する為、クロスボビドンとの配合時には、抗酸化剤を含有させてもよい。

抗酸化剤は、例えば、亜硫酸ナトリウム、ピロ亜硫酸ナトリウム、ビタミンE類、ロンガリット、チオグリセロール、チオ硫酸ナトリウム、アスコルビン酸塩、アセチルシステインなどが挙げられるが、これらに限定される訳ではない。

また本発明は、式1で示されるベンズイミダゾール系化合物に炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム、アミノアルキルメタアクリレートコポリマーE、アルギニンアスパラギン酸塩、ヒドロキシプロピルセルロース及びクロスボビドンから選ばれる1種以上の物質を配合してなる核に腸溶性皮膜を被覆した製剤である。本発明において、核とは、錠剤、顆粒剤などを意味する。また、本発明は、精製白糖、白糖・デンプン混合物若しくは結晶セルロース等から成る球状顆粒をシード顆粒として、ベンズイミダゾール系化合物と炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム、アミノアルキルメタアクリレートコポリマーE、アルギニンアスパラギン酸塩、ヒドロキシプロピルセルロース及びクロスボビドンから選ばれる1種以上の物質を層積又はコーティングしてなる核に腸溶性皮膜を被覆した製剤も含むものである。ベンズイミダゾール系化合物は酸性状態において極めて不安定であり、ベンズイミダゾール系化合物を服用した場合、胃内において胃酸と接触すると直ちに分解し、その生理活性を失う。したがって、胃内における分解を防ぐためには胃内で溶解しない製剤、すなわちベンズイミダゾール系化合物を含む核に腸溶性の物質を被覆した製剤とする必要があるのである。

さらに本発明は、式1で示されるベンズイミダゾール系化合物に炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム、アミノアルキルメタア

クリレートコポリマーE、アルギニンアスパラギン酸塩、ヒドロキシプロピルセルロース及びクロスポビドンから選ばれる1種以上の物質を配合してなる核に中間皮膜を被覆し、更に腸溶性皮膜を被覆した製剤である。腸溶性皮膜は一般に酸性物質であるため、ベンズイミダゾール系化合物との直接接触は好ましくない。そこでベンズイミダゾール系化合物を含有する核と腸溶性皮膜の中間に、不活性な中間皮膜を施すことができる。ここで不活性とはベンズイミダゾール系化合物の安定性に悪影響を及ぼさない物質である。不活性な中間皮膜は水溶性高分子、水溶解性若しくは水分散性物質、水不溶性物質のいずれでもよく具体的には、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、アミノアルキルメタアクリレートコポリマーE、乳糖、マンニトール、デンプン、結晶セルロース、エチルセルロース、酢酸ビニル等を挙げることができる。なお、特開平1-290628号公報に開示されているように、水不溶性物質で中間皮膜を施す場合には、皮膜中に水不溶性の微粒子を混合してもよい。

本発明は、また、上記の腸溶性皮膜を被覆した製剤に、防湿性皮膜を被覆してもよい。防湿性皮膜とは、水蒸気の通過を抑制する皮膜のことであり、機能的には、皮膜自体が水蒸気の透過性を抑制する皮膜や皮膜中に水蒸気を捕獲して内部への水蒸気の流入を抑制する皮膜等が挙げられる。

防湿性皮膜は、ベンズイミダゾール系化合物への水分の侵入を防御して安定性を向上させると共に、微粉碎化したクロスポビドンの吸湿時の膨潤に由来する錠剤のひび割れや変形を防止する機能を有している。

防湿性皮膜は、水溶性皮膜でも水不溶性皮膜でも良く、例えば、ポリビニルアセタールジエチルアミノアセテート、HA三共（ポリビニルアセタールジエチルアミノアセテート、ヒドロキシプロピルメチルセルロース、ステアリン酸、フマル酸の混合物）、ポリビニルアルコールなどから成る皮膜や、ヒドロキシプロピルセルロース、ヒドロキシプロピルメチルセルロース、エチルセルロースなどのセルロース誘導体を1種以上配合してなる皮膜、及び/又は白糖を主成分とする糖衣皮膜などが挙げられるが、これらに限定される訳ではない。

防湿性皮膜は、ベンズイミダゾール系化合物にとどまらず、同様の化学的性質

を有する薬物を含有する製剤にも有用である。即ち、水分存在下で分解が促進され、且つ胃酸との接触時にも分解促進が認められる薬物を含有する製剤において効果が顕著に認められる。

即ち、本発明は、水分存在下で分解が促進され且つ胃酸中で化学的に不安定な薬物を配合してなる核に腸溶性皮膜を被覆し、更に防湿性皮膜を被覆した製剤である。また、腸溶性皮膜と防湿性皮膜の間に、中間皮膜を被覆してもよい。

本発明においては、式 1 で表されるベンズイミダゾール系化合物が、ラベプラゾールである場合に、特に優れた効果を示す。

即ち、本発明は、好ましくは、式 3 で示されるラベプラゾール又はそのアルカリ金属塩に、水酸化ナトリウム、水酸化カリウム及び/又は炭酸ナトリウムを配合してなる組成物である。

また、本発明は、好ましくは、式 3 で示されるラベプラゾール又はそのアルカリ金属塩に、1) クロスポビドンと 2) 水酸化ナトリウム、水酸化カリウム及び/又は炭酸ナトリウムを配合してなる組成物である。

クロスポビドンは、前述のように、平均粒径を数 μm ~ 50 μm に微粉碎したものを使用することが好ましい。また、抗酸化剤は、前述のようにクロスポビドン中に含まれる極微量の過酸化物の影響を防止する為に添加してもよい。したがって、ラベプラゾール又はそのアルカリ金属塩に 1) クロスポビドンと 2) 水酸化ナトリウム、水酸化カリウム及び/又は炭酸ナトリウムを配合してなる組成物中に、抗酸化剤を配合してもよい。

本発明は、また、好ましくは、式 3 で示されるラベプラゾール又はそのアルカリ金属塩に 1) クロスポビドンと 2) 水酸化ナトリウム、水酸化カリウム及び/又は炭酸ナトリウムを配合してなる核に腸溶性皮膜を被覆した製剤である。

さらに、本発明は、好ましくは、式 3 で示されるラベプラゾール又はそのアルカリ金属塩に 1) クロスポビドンと 2) 水酸化ナトリウム、水酸化カリウム及び/又は炭酸ナトリウムを配合してなる核に中間皮膜を被覆し、更に腸溶性皮膜を被覆した製剤である。

本発明は、また、好ましくは、式 3 で示されるラベプラゾール又はそのアルカ

り金属塩に1) クロスボビドンと2) 水酸化ナトリウム、水酸化カリウム及び/又は炭酸ナトリウムを配合してなる核に中間皮膜を被覆し、更に腸溶性皮膜を被覆し、次に防湿性皮膜を被覆した製剤である。

本発明に係る組成物又は製剤は、通常用いられる方法により製造することができる。

即ち、例えば、ベンズイミダゾール系化合物又はそのアルカリ金属塩に炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム、アミノアルキルメタアクリレートコポリマーE、アルギニンアスパラギン酸塩、ヒドロキシプロピルセルロース及びクロスボビドンから選ばれる1種以上の物質を配合し、賦形剤を加えて乾式又は湿式造粒を行い、必要に応じてクロスボビドン等の崩壊剤を加えて打錠し製することができる。また、例えば、ベンズイミダゾール系化合物又はそのアルカリ金属塩に、炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム、アミノアルキルメタアクリレートコポリマーE、アルギニンアスパラギン酸塩、ヒドロキシプロピルセルロース及びクロスボビドンから選ばれる1種以上の物質を高密度に配合したベンズイミダゾール含有顆粒とベンズイミダゾール系化合物を含有しないプラセボ顆粒を調製後に、両顆粒を混合し、必要に応じてクロスボビドン等の崩壊剤を加えて打錠してもよい。もちろん、これらの方法に限定される訳ではない。

具体例として、例えば、ベンズイミダゾール系化合物であるラベプラゾールナトリウム100g、炭酸ナトリウム30g、マンニトール130gを混合し、さらに混合しながらエタノールに溶解したヒドロキシプロピルセルロースを徐々に加えて造粒し、乾燥後24メッシュ篩で篩過する。これにクロスボビドン30g、ステアリン酸カルシウム2gを加えて混合後打錠して1錠135mgの錠剤を得ることができる。

この錠剤に、流動層装置を用いてヒドロキシプロピルセルロースのエタノール溶液を噴霧し、さらに、ヒドロキシプロピルメチルセルロースフタレート又は腸溶性メタアクリル酸コポリマーの水/エタノール溶液を噴霧して中間皮膜を施した腸溶錠を製造することができる。

本発明によると非常に不安定なベンズイミダゾール系化合物の安定化が可能である。その効果例を以下に示す。

実験例

ラベプラゾールナトリウム 50 mg と下記の表に示す添加剤 450 mg を乳鉢で混合した。

これを透明なガラス瓶に入れ、冷所、60℃及び40℃相対湿度75%で1週間保存し、高速液体クロマトグラフィーにより含量を測定した。冷所保存品の含量を100%としたときの各条件下における残存率を表1から3に示した。また、色の着色変化について目視で評価した。ラベプラゾールナトリウムは、表1では非晶質、表2と表3では結晶質を使用した。なお、表1においては対照として非晶質ラベプラゾールナトリウム単独のほかに崩壊剤として使用される低置換度ヒドロキシプロピルセルロース（表中L-HPCと表示）を配合したものをを用い、表2においてはさらに制酸剤として使用されるアルカリ性無機塩である水酸化アルミニウム（表中Al(OH)₃と表示）を配合したものをを用い、表3においては結合剤として用いられるポリビニルピロリドン（表中PVPと表示）を配合した試料を用いた。

表1 ラベプラゾールナトリウムの接触試験

		60°C	40°C-75%RH
対照	ラベプラゾールナトリウム（非晶質）	99.1	93.9
	ラベプラゾールナトリウム+L-HPC	80.4	73.3
本願	ラベプラゾールナトリウム+クロスボビドン	98.1	90.4

単位：%

表2 ラベプラゾールナトリウム（結晶質）の接触試験

		60°C	40°C-75%RH
対照	ラベプラゾールナトリウム（結晶質）	99.8	91.8
	ラベプラゾールナトリウム+L-HPC	62.2	75.0
	ラベプラゾールナトリウム+Al(OH) ₃	36.9	26.2
本願	ラベプラゾールナトリウム+クロスボビドン	93.3	89.5
	ラベプラゾールナトリウム+Na ₂ CO ₃	99.1	90.3
	ラベプラゾールナトリウム+Arg・Asp	97.5	90.7

単位：%

表3 ラベプラゾールナトリウム（結晶質）の接触試験

		60°C	40°C-75%RH
対照	ラベプラゾールナトリウム（結晶質）	97.3	86.9
	ラベプラゾールナトリウム+PVP	89.5	67.7
本願	ラベプラゾールナトリウム	92.0	86.9
	+ヒドロキシプロピルセルロース		
	ラベプラゾールナトリウム+Na ₂ CO ₃	93.0	82.8
	ラベプラゾールナトリウム+NaOH	91.6	98.8
	ラベプラゾールナトリウム+KOH	92.6	96.8
	ラベプラゾールナトリウム+オイドラギットE	102.4	86.0
	ラベプラゾールナトリウム+K ₂ CO ₃	104.5	81.3

単位：％

本願発明に係る配合試料の着色変化は、いずれも対照と比較して小さかった。さらに、表1～3の含量安定性の結果から、本願発明に係る炭酸ナトリウム（表中Na₂CO₃と表示）、炭酸カリウム（表中K₂CO₃と表示）、水酸化ナトリウム（表中NaOHと表示）、水酸化カリウム（表中KOHと表示）、アミノアルキルメタアクリレートコポリマーE（表中オイドラギットE（登録商標）と表示）、アルギニン・アスパラギン酸塩（表中Arg・Aspと表示）、ヒドロキシプロピルセルロース及びクロスボビドンは、ベンズイミダゾール系化合物を安定化することが明らかである。

錠剤中の炭酸ナトリウムの効果

下記に示す実施例4～9で得られた炭酸ナトリウム添加量の異なる錠剤を、40℃相対湿度75％で1週間保存した後に、高速液体クロマトグラフィーにより測定した錠剤中のラベプラゾールナトリウム含量を表4に示した。

表4 湿式造粒法による錠剤処方安定性評価

処方	実施例4	実施例5	実施例6	実施例7	実施例8	実施例9
(1週間)						
冷所	99.4	99.0	98.7	99.4	99.5	98.9
40°C-75%RH	83.8	85.7	85.1	92.5	92.8	95.5
(1ヶ月)						
冷所	99.7	99.7	99.7	99.7	99.7	99.6
25°C-75%RH	97.8	98.5	98.3	99.2	99.3	99.3

単位：％

炭酸ナトリウムの添加量に依存して錠剤中のラベプラゾールナトリウム含量安定性が向上することから、本発明における炭酸ナトリウムの添加効果は明らかである。

錠剤中のクロスボビドンの効果

下記に示す実施例 10～12 で得られたクロスボビドン粉末の添加量の異なる錠剤を、40℃相対湿度75%で1週間保存した後に、高速液体クロマトグラフィーにより測定した錠剤中のラベプラゾールナトリウム含量を表5に示した。また、錠剤の色の変化に関しては、クロスボビドン粉末の添加量が多いほど、錠剤の着色変化が少なかった。

表5 湿式造粒法によるクロスボビドン添加錠剤の安定性

処方	実施例 10	実施例 11	実施例 12
(1週間)			
冷所	99.7	99.7	99.7
40℃-75%RH	97.8	98.5	98.3
(1ヶ月)			
冷所	99.4	99.0	98.7
40℃-75%RH	83.8	85.7	85.1

単位：%

クロスボビドンを添加するとベンゾイミダゾール系化合物の安定性が向上することは、明らかである。

錠剤中の微粉化クロスボビドンの効果

下記に示す実施例 16～18 で得られた平均粒径の異なるクロスボビドンを添加した錠剤の厚さを、冷所及び25℃相対湿度75%で各々1ヶ月保存した後に測定し、25℃相対湿度75%保存錠剤の冷所保存錠剤に対する膨張率を評価した。その結果、平均粒径51μm、12μm、6μmのクロスボビドンを含有する錠剤の膨張率は、各々、1.61、1.48、1.43であった。

クロスボビドンは、平均粒径の小さい微粉にするほど、錠剤の膨潤度が減少する為、錠剤の膨張に起因するひびわれや変形が少なくなる。したがって、クロスボビドンの微粉化が、錠剤の形状の安定性向上に寄与することは、明らかである。

腸溶性皮膜を被覆した製剤に施した防湿性皮膜の効果

下記に示す実施例 19～20 で得られた腸溶性皮膜被覆錠剤、腸溶性皮膜と防湿性皮膜の両者を被覆した錠剤を、25℃相対湿度75%で1週間保存した後に、錠剤中のラベプラゾールの類縁物質量を高速液体クロマトグラフィーで測定した。その結果、腸溶性皮膜被覆錠剤、腸溶性皮膜と防湿性皮膜の両者を被覆した錠剤の類縁物質量は、各々、2.88%、2.23%であった。

腸溶性皮膜と防湿性皮膜の両者を被覆した製剤は、腸溶性皮膜被覆錠剤と比較して同等若しくはそれ以上の安定性を有することは、明らかである。

下記に示す実施例 21～23 で得られたプラセボ錠剤の厚さを、冷所及び40℃相対湿度75%で各々1週間保存した後に測定し、40℃相対湿度75%保存錠剤の冷所保存錠剤に対する膨張率を評価した。その結果、腸溶性皮膜被覆錠剤、腸溶性皮膜被覆錠剤に白糖から成る防湿性皮膜を被覆した錠剤、腸溶性皮膜被覆錠剤にHA（三共）（ポリビニルアセタールジエチルアミノアセテート、ヒドロキシピロピルメチルセルロース、マクロゴール、タルクの混合物）から成る防湿性皮膜を被覆した錠剤の膨張率は、各々、1.15、1.03、1.12であった。

腸溶性皮膜と防湿性皮膜の両者を被覆した製剤は、腸溶性皮膜被覆錠剤と比較して保存時の錠剤の膨潤度が小さい為、錠剤の形状の安定性が向上することは、明らかである。

ベンズイミダゾール系化合物を含有する核部分に添加する抗酸化剤の効果

下記に示す実施例 24～26 で得られた、含有過酸化物量の異なるクロスボビドンを追加した錠剤を用いて、高速液体クロマトグラフィーにより錠剤中のラベプラゾールナトリウムの類縁物質量を測定した。その結果、過酸化物含量が18 ppm、190 ppm、310 ppmであるクロスボビドンを追加した錠剤の初期類縁物質量は、各々0.65%、0.88%、1.13%であり、クロスボビドン中に含有される過酸化物量が多いほど、ラベプラゾールナトリウムの分解が促進され類縁物質量の増加が認められた。

また、含有過酸化物量が201 ppmであるクロスボビドン1gを精秤し、亜硫酸

ナトリウムを添加（添加量：未添加、0.02%、0.05%、0.10%の4水準）してよく混合した後に、混合物中の過酸化物量を日本薬局方記載の試験法に従って測定した。その結果、亜硫酸ナトリウムの添加量が、未添加、0.02%、0.05%、0.10%である組成物中の過酸化物量は、各々、201 ppm、184 ppm、108 ppm、0 ppmであり、亜硫酸ナトリウム添加量が多くなるほど、過酸化物量の減少が認められた。

以上のことから、ベンズイミダゾール系化合物とクロスポビドンを含有する錠剤の核部分に抗酸化剤を添加することにより、製剤中のベンズイミダゾール系化合物の安定性が向上することは、明らかである。

実施例

以下に実施例を挙げて本発明を更に詳細に説明するが、本発明がこれらに限定されるわけではない。

実施例 1

ラベプラゾールナトリウム10gに炭酸ナトリウム10g及びマンニトール100gを加え混合しながら、エタノールに溶解したヒドロキシプロピルセルロース2.5gを徐々に加え造粒し、乾燥後篩過してステアリン酸カルシウムを添加し打錠してラベプラゾールナトリウムを10mg含む1錠120mgの錠剤を得た。

実施例 2

実施例1で得た錠剤に、水エタノールの2：8混合溶媒にヒドロキシプロピルメチルセルロースフタレート10gを溶解した溶液を流動層造粒装置を用いてスプレーし腸溶錠を製造した。

実施例 3

実施例1で得た錠剤に、流動層造粒装置を用いてヒドロキシプロピルセルロースのエタノール溶液をスプレーした後、実施例2と同様に操作して腸溶錠を得た。

実施例 4～9

ラベプラゾールナトリウム10gに炭酸ナトリウム0～10g及びマンニトール15～90gを各々加え混合しながら、エタノールに溶解したヒドロキシプロ

ピルセルロース 0.7 ~ 2 g を徐々に加え攪拌湿式造粒をし、主薬顆粒を調製した。また、別に、マンニトール 100 g にエタノールに溶解したヒドロキシプロピルセルロース 2 g を徐々に加えながら攪拌湿式造粒を行い、プラセボ顆粒を調製した。次に主薬顆粒とプラセボ顆粒を混合し、クロスポビドン 5 % と微量のステアリン酸マグネシウムを粉添後、打錠してラベプラゾールナトリウムを 10 mg 含む 1 錠 100.5 mg の錠剤を得た。各処方を表 6 に示した。

表6 湿式造粒法による錠剤処方

処方	実施例 4	実施例 5	実施例 6	実施例 7	実施例 8	実施例 9
主薬顆粒						
ラベプラゾールナトリウム (結晶質)	10.0	10.0	10.0	10.0	10.0	10.0
無水Na ₂ CO ₃	-	-	-	5.0	5.0	10.0
マンニトール	82.0	30.0	20.0	25.0	15.0	20.0
ヒドロキシプロピルセルロース	2.0	1.0	0.7	1.0	0.7	1.0
(小計)	94.0	41.0	30.7	41.0	30.7	41.0
プラセボ顆粒						
マンニトール	-	52.0	62.1	52.0	62.1	52.0
ヒドロキシプロピルセルロース	-	1.0	1.2	1.0	1.2	1.0
(小計)	0.0	53.0	63.3	53.0	63.3	53.0
粉添部						
クロスボビドン	5.0	5.0	5.0	5.0	5.0	5.0
ステアリン酸マグネシウム	1.5	1.5	1.5	1.5	1.5	1.5
(小計)	6.5	6.5	6.5	6.5	6.5	6.5
総計	100.5	100.5	100.5	100.5	100.5	100.5

単位: mg

実施例 10～12

粉添クロスボビドン量を 0、2.5、5% の 3 水準とり、その他は実施例 4～9 と同様の方法で錠剤を得た。処方を表 7 に示した。

表7 湿式造粒法によるクロスボビドン添加の錠剤処方

処方		実施例 10	実施例 11	実施例 12
主薬顆粒	ラベプラゾールナトリウム（結晶質）	10.0	10.0	10.0
	無水Na ₂ CO ₃	5.0	5.0	5.0
	マンニトール	25.0	25.0	25.0
	ヒドロキシプロピルセルロース	1.0	1.0	1.0
	（小計）	41.0	41.0	41.0
プラセボ顆粒	マンニトール	56.9	54.4	52.0
	ヒドロキシプロピルセルロース	1.1	1.1	1.0
	（小計）	58.0	55.5	53.0
粉添部	クロスボビドン	-	2.5	5.0
	ステアリン酸マグネシウム	1.5	1.5	1.5
	（小計）	1.5	4.0	6.5
総計		100.5	100.5	100.5

単位：mg

実施例 13～14

表 8 に示す 2 処方例に従って、ラベプラゾールナトリウム 100 g に炭酸ナトリウム 0～50 g、マンニトール 79.3～84.3 g、クロスボビドン 4.2 g 及びステアリン酸マグネシウム 1.5 g を各々加え十分に混合して、直接打錠を行いラベプラゾールナトリウム 10 mg 含む 1 錠 100 mg の錠剤を得た。

表8 直接打錠法による錠剤処方

処方	実施例 13	実施例 14
ラベプラゾールナトリウム（結晶質）	10.0	10.0
無水Na ₂ CO ₃	-	5.0
マンニトール	84.3	79.3
クロスボビドン	4.2	4.2
ステアリン酸マグネシウム	1.5	1.5
総計	100.0	100.0

単位：mg

実施例 15

ラベプラゾールナトリウム 100 g に炭酸ナトリウム 50 g 及びステアリン酸マグネシウム 2 g を各々加えよく混合して乾式圧縮造粒し、主薬顆粒を調製した。また、別に、マンニトール 76.3 g 及びクロスポビドン 4.2 g を各々加えよく混合してエタノールに溶解したヒドロキシプロピルセルロース 2.3 g を徐々に加えながら攪拌湿式造粒を行い、プラセボ顆粒を調製した。次に主薬顆粒とプラセボ顆粒を混合し、微量のステアリン酸マグネシウムを粉添後、打錠して表 9 に示すようにラベプラゾールナトリウムを 10 mg 含む 1 錠 100 mg の錠剤を得た。

表 9 乾式造粒法による錠剤処方

処方		実施例 15
主薬顆粒	ラベプラゾールナトリウム (結晶質)	10.0
	無水 Na_2CO_3	5.0
	ステアリン酸マグネシウム	0.2
	(小計)	15.2
プラセボ顆粒	マンニトール	76.8
	クロスポビドン	4.2
	ヒドロキシプロピルセルロース	2.3
	(小計)	83.3
粉添部	ステアリン酸マグネシウム	1.5
総計		100.0

単位: mg

実施例 16 ~ 18

ラベプラゾールナトリウム 100 g に平均粒径の異なるクロスポビドン 527 g 及びヒドロキシプロピルセルロース 20 g をを混合し、3 g のステアリン酸マグネシウムを粉添後、打錠して表 10 に示すようにラベプラゾールナトリウムを 10 mg 含む 1 錠 65 mg の錠剤を得た。尚、使用したクロスポビドンは、BASF 社の製品であり、その平均粒径は、コリドン CL ($51 \mu\text{m}$)、コリドン CLM ($12 \mu\text{m}$)、コリドン CLM のハンマーミル粉碎品 ($6 \mu\text{m}$) である。

表 10 平均粒径の異なるクロスボビドン添加の処方

処方	実施例 16	実施例 17	実施例 18
ラベプラゾールナトリウム	10.0	10.0	10.0
クロスボビドン (コリドンCL)	52.7	-	-
クロスボビドン (コリドンCLM)	-	52.7	-
クロスボビドン (コリドンCLMの粉碎品)	-	-	52.7
ヒドロキシプロピルセルロース	2.0	2.0	2.0
ステアリン酸マグネシウム	0.3	0.3	0.3
(小計)	65.0	65.0	65.0

単位 : mg

注) 平均粒径

クロスボビドン (コリドンCL) : 51 μ mクロスボビドン (コリドンCLM) : 12 μ mクロスボビドン (コリドンCLMの粉碎品) : 6 μ m

実施例 19 ~ 20

ラベプラゾールナトリウムを含有する核部分をエタノールで造粒後、エチルセルロース、クロスボビドン、ステアリン酸マグネシウムを含有する水不溶性の中間皮膜をコーティングした。次に、更なる皮膜を施すことにより、腸溶性皮膜被覆錠剤と腸溶性皮膜、防湿性皮膜の両者を被覆した錠剤を得た。尚、処方は、表 11 に示した。

表 1 1 腸溶性製剤及び防湿性皮膜を施した製剤の処方

処方		実施例 19	実施例 20
核部分	ラベプラゾールナトリウム	10.0	10.0
	マンニトール	36.2	36.2
	クロスポビドン	15.6	15.6
	水酸化ナトリウム	0.1	0.1
	無水炭酸ナトリウム	5.0	5.0
	ヒドロキシプロピルセルロース	2.0	2.0
	ステアリン酸マグネシウム	1.1	1.1
	(小計)	70.0	70.0
中間皮膜	エチルセルロース	0.5	0.5
	クロスポビドン	1.0	1.0
	ステアリン酸マグネシウム	0.1	0.1
	(小計)	1.6	1.6
腸溶性皮膜	ヒドロキシプロピルメチルセルロースフタレート	8.0	8.0
	モノグリセライド	0.8	0.8
	タルク	0.75	0.75
	酸化チタン	0.4	0.4
	黄色酸化鉄	0.05	0.05
	(小計)	10.0	10.0
防湿性皮膜	ヒドロキシプロピルメチルセルロース	-	3.0
	マクロゴール	-	0.6
	タルク	-	1.4
	(小計)		5.0
総計		81.6	86.6

単位 : mg

実施例 2 1 ~ 2 3

ベンズイミダゾール系化合物を含有しないプラセボ錠として、核部分にヒドロキシプロピルセルロースから成る水溶性中間皮膜を施した錠剤を調製した。この錠剤に腸溶性皮膜をコーティングした腸溶性皮膜被覆錠剤、腸溶性皮膜被覆錠剤に白糖又はHA（三共）から成る溶液をスプレーした防湿性皮膜被覆製剤を調製した。尚、処方表は表 1 2 に示した。

表 1 2 プラセボ処方

	処方	実施例 2 1	実施例 2 2	実施例 2 3
核部分	マンニトール	31.8	31.8	31.8
	クロスボビドン (コリドン C L M)	27.7	27.7	27.7
	ヒドロキシプロピルセルロース	5.0	5.0	5.0
	ステアリン酸マグネシウム	0.5	0.5	0.5
	(小計)	65.0	65.0	65.0
中間皮膜	ヒドロキシプロピルセルロース	3.0	3.0	3.0
腸溶性皮膜	ヒドロキシプロピルメチルセルロースフタレート	8.0	8.0	8.0
	モノグリセライド	0.8	0.8	0.8
	タルク	0.75	0.75	0.75
	酸化チタン	0.4	0.4	0.4
	黄色酸化鉄	0.05	0.05	0.05
	(小計)	10.0	10.0	10.0
防湿性皮膜	白糖	-	10.0	-
	HA (三共) *	-	-	10.0
総計		78.0	88.0	88.0

単位 : m g

注 : HA (三共) *
 ポリビニルアセタールジエチルアミノアセテート、
 ヒドロキシプロピルメチルセルロース、
 マクロゴール、タルクの混合物

実施例 2 4 ~ 2 6

ラベプラゾールナトリウムと過酸化物量の異なるクロスボビドン、水酸化ナトリウム及び炭酸ナトリウムを含有する錠剤を、表 1 3 の処方に従って、湿式造粒法により得た。

表 1 3 過酸化物含量の異なるクロスボビドンを含有する処方

処方	実施例 2 4	実施例 2 5	実施例 2 6
ラベプラゾールナトリウム	10.0	10.0	10.0
マンニトール	36.9	36.9	36.9
クロスボビドン (INF-10) * 1	14.0	-	-
クロスボビドン (INF-10) * 2	-	14.0	-
クロスボビドン (コリドン CLM) * 3	-	-	14.0
クロスボビドン (コリドン CL)	14.0	14.0	14.0
水酸化ナトリウム	0.5	0.5	0.5
無水炭酸ナトリウム	2.5	2.5	2.5
ヒドロキシプロピルセルロース	2.0	2.0	2.0
ステアリン酸マグネシウム	1.1	1.1	1.1
(計)	70.0	70.0	70.0

単位: mg

注)

クロスボビドン (INF-10) * 1 : (過酸化物含量: 18 ppm)

クロスボビドン (INF-10) * 2 : (過酸化物含量: 190 ppm)

クロスボビドン (コリドン CLM) * 3 : (過酸化物含量: 310 ppm)

実施例 2 7

ラベプラゾールナトリウム 30 g に微粉クロスボビドン 43.5 g、ヒドロキシプロピルセルロース 6 g を加え十分に混合しながら、水酸化ナトリウムのエタノール溶液（水酸化ナトリウム 1.5 g をエタノールに溶解させた溶液）を徐々に加え造粒し、乾燥後、小型スピードミルで整粒する。整粒顆粒に、3% のクロスボビドンと 1.6% のステアリン酸マグネシウムを添加し混合して打錠し、ラベプラゾールナトリウムを 10 mg 含む 1 錠 70 mg の錠剤を得た。

実施例 2 8

実施例 2 7 で得た錠剤に、流動層造粒装置を用いてヒドロキシプロピルセルロースと微量のステアリン酸マグネシウムを含有する含水エタノール液をコーティングし、中間皮膜 2 mg が層積された錠剤を得た。次に、中間皮膜被覆錠剤に、ヒドロキシプロピルセルロースフタレート、モノグリセライド、タルク及び酸化チタンを含有する含水エタノール液を流動層造粒装置を用いてスプレーし、腸溶性皮膜 10 mg が被覆された腸溶錠を得た。

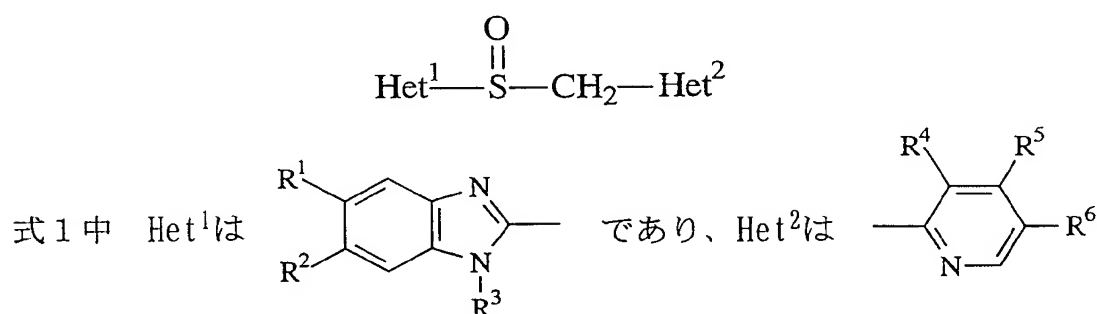
実施例 29

実施例 28 で得た腸溶錠に、流動層造粒装置を用いてヒドロキシプロピルメチルセルロース、マクロゴール 6000 及びタルクを含有する精製水をスプレーし、防湿性皮膜 5 mg が被覆された錠剤を得た。

請求の範囲

1. (A) 下記構造式(式1)で示されるベンズイミダゾール系化合物又はそのアルカリ金属塩および(B)炭酸ナトリウム、炭酸カリウム、水酸化ナトリウム、水酸化カリウム、アミノアルキルメタアクリレートコポリマーE、アルギニンアスパラギン酸塩、ヒドロキシプロピルセルロース及びクロスボビドンからなる群より選ばれる少なくとも1種の物質を含む医薬組成物。

式1



であり、R¹およびR²は同じかまたは異なっていて、水素、メトキシ及びジフルオロメトキシから選択され、R³は水素及びナトリウムから選択され、R⁴、R⁵およびR⁶は同じかまたは異なっていて、水素、メチル、メトキシ、メトキシプロポキシ及びトリフルオロエトキシから選択される。

2. ベンズイミダゾール系化合物がラベプラゾール、オメプラゾール、パントプラゾールまたはランソプラゾールである請求項1記載の組成物。

3. 1重量部の(A)と0.01~20重量部の(B)とを含む請求項1記載の組成物。

4. 請求項1に定義した組成物よりなる核および腸溶性皮膜よりなる医薬製剤。

5. 請求項1に定義した組成物よりなる核、中間皮膜および腸溶性皮膜よりなる医薬製剤。

6. 請求項1に定義した組成物よりなる核、中間皮膜、腸溶性皮膜及び防湿性皮膜よりなる医薬製剤。

7. (A)がラベプラゾール又はそのアルカリ金属塩であり、(B)が水酸化ナトリウム、水酸化カリウム及び炭酸ナトリウムよりなる群より選ばれた少なくとも1種

である請求項 1 記載の組成物。

8. (A) がラベプラゾール又はそのアルカリ金属塩であり、(B) が (1) クロスボビドンおよび (2) 水酸化ナトリウム、水酸化カリウム及び炭酸ナトリウムよりなる群より選ばれた少なくとも 1 種である請求項 1 記載の組成物。

9. 請求項 8 に定義した組成物よりなる核および腸溶性皮膜よりなる医薬製剤。

10. 請求項 8 に定義した組成物よりなる核、中間皮膜および腸溶性皮膜よりなる医薬製剤。

11. 請求項 8 に定義した組成物よりなる核、中間皮膜、腸溶性皮膜及び防湿性皮膜よりなる医薬製剤。

12. 抗酸化剤をさらに含む請求項 8 記載の組成物。

13. 核がさらに抗酸化剤を含む請求項 9 ～ 11 のいずれかに記載した医薬製剤。

14. 水分存在下で分解が促進され且つ胃酸中で化学的に不安定な薬物を配合してなる核に腸溶性皮膜を被覆し、更に防湿性皮膜を被覆した製剤。

15. 水分存在下で分解が促進され且つ胃酸中で化学的に不安定な薬物を配合してなる核に中間皮膜を被覆し、更に腸溶性皮膜を被覆し、次に防湿性皮膜を被覆した製剤。

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP99/02098

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl⁶ A61K31/44, A61K9/28, A61K47/02, A61K47/32, A61K47/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl⁶ A61K31/44, A61K9/28, A61K47/02, A61K47/32, A61K47/38

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	WO, 9222284, A1 (Byk Gulden Lomberg Chemische Fabrik GmbH.), 23 December, 1992 (23. 12. 92) & JP, 6-508118, A & EP, 589981, A2	1-6 7-15
X Y	JP, 9-511257, A (Esteve Quimica S.A.), 11 November, 1997 (11. 11. 97) & WO, 9623500, A1 & US, 5626875, A	1-6 7-15
A Y	JP, 9-216847, A (Amano Pharmaceutical Co., Ltd.), 19 August, 1997 (19. 08. 97) (Family: none)	1-13 14, 15
X Y	Drug Development and Industrial Pharmacy, vol. 18, no. 13, p1437-1447, 1992, Teturo Tabata et al., "STABILIZATION OF A NEW ANTIULCER DRUG (LANSOPRAZOLE) IN THE SOLID DOSAGE FORMS" Particularly refer to page 1442 ; Table 5	1-6 7-15

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier document but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search
12 July, 1999 (12. 07. 99)Date of mailing of the international search report
21 July, 1999 (21. 07. 99)Name and mailing address of the ISA/
Japanese Patent Office

Authorized officer

Facsimile No.

Telephone No.

A. 発明の属する分野の分類 (国際特許分類 (IPC))

Int. Cl^o A61K31/44, A61K9/28, A61K47/02, A61K47/32
A61K47/38

B. 調査を行った分野

調査を行った最小限資料 (国際特許分類 (IPC))

Int. Cl^o A61K31/44, A61K9/28, A61K47/02, A61K47/32
A61K47/38

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース (データベースの名称、調査に使用した用語)

CA (STN)

C. 関連すると認められる文献

引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
X Y	WO, 9222284, A1 (ビイグ グルテン コンベルグ ヒエミツシ フアブリーク ケゼルシャフ ト ミット ベシュレンゲル ハフツング) 23. 12月. 1992 (23. 12. 92) & JP, 6-508118, A & EP589981, A2	1-6 7-15
X Y	JP, 9-511257, A (エステベ・キカ・エス・エー) 11. 11月. 1997 (11. 11. 97) & WO, 9623500, A1 & US, 5626875, A	1-6 7-15
A Y	JP, 9-216847, A (天野製薬株式会社) 19. 8月. 1997 (19. 08. 97) ファミ リーなし	1-13 14, 15
X Y	Drug Development and Industrial Pharmacy, vol. 18, no. 13, p1437- 1447, 1992, Teturo Tabata et al, 「STABILIZATION OF A NEW ANTIUL	1-6 7-15

☐ C欄の続きにも文献が列挙されている。☐ パテントファミリーに関する別紙を参照。

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国際調査を完了した日

12. 07. 99

国際調査報告の発送日

21.07.99

国際調査機関の名称及びあて先

日本国特許庁 (ISA/J P)

郵便番号 100-8915

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特許庁審査官 (権限のある職員)

鶴見 秀紀

印

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8415

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C (続き) . 関連すると認められる文献		
引用文献の カテゴリー*	引用文献名 及び一部の箇所が関連するときは、その関連する箇所の表示	関連する 請求の範囲の番号
	CER DRUG (LANSOPRAZOLE) IN THE SOLID DOSAGE FORMS」特にp1442. table5参照	



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 471/04, A61K 31/435	A1	(11) International Publication Number: WO 99/55705 (43) International Publication Date: 4 November 1999 (04.11.99)		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> (21) International Application Number: PCT/SE99/00662 (22) International Filing Date: 23 April 1999 (23.04.99) (30) Priority Data: 9801526-6 29 April 1998 (29.04.98) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): AMIN, Kosrat [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). DAHLSTRÖM, Mikael [FI/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). NORDBERG, Peter [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). STARKE, Ingemar [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE). </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i> <i>Under Rule 91.1(f), with a request for rectification.</i> </td> </tr> </table>			(21) International Application Number: PCT/SE99/00662 (22) International Filing Date: 23 April 1999 (23.04.99) (30) Priority Data: 9801526-6 29 April 1998 (29.04.98) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): AMIN, Kosrat [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). DAHLSTRÖM, Mikael [FI/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). NORDBERG, Peter [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). STARKE, Ingemar [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i> <i>Under Rule 91.1(f), with a request for rectification.</i>
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(54) Title: IMIDAZO PYRIDINE DERIVATIVES WHICH INHIBIT GASTRIC ACID SECRETION				
<div style="position: absolute; left: 620px; top: 615px;">(I)</div>				
(57) Abstract <p>The present invention relates to imidazo pyridine derivatives of formula (I), in which the phenyl moiety is substituted, and in which the imidazo pyridine moiety is substituted with carboxamide group in 6-position, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases.</p>				

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IMIDAZO PYRIDINE DERIVATIVES WHICH INHIBIT GASTRIC ACID SECRETION

TECHNICAL FIELD

5 The present invention relates to novel compounds, and pharmaceutically acceptable salts thereof, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions
10 containing at least one compound of the invention, or a pharmaceutically acceptable salt thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above. The invention also relates to new intermediates for in the preparation of the novel compounds.

15 BACKGROUND ART

Substituted imidazo[1,2-a]pyridines, useful in the treatment of peptic ulcer diseases, are known in the art, e.g. from EP-B-0033094 and US 4,450,164 (Schering Corporation); from EP-B-0204285 and US 4,725,601 (Fujisawa Pharmaceutical Co.); and from publications by
20 J. J. Kaminski et al. in the Journal of Medical Chemistry (vol. 28, 876-892, 1985; vol. 30, 2031-2046, 1987; vol. 30, 2047-2051, 1987; vol. 32, 1686-1700, 1989; and vol. 34, 533-541, 1991).

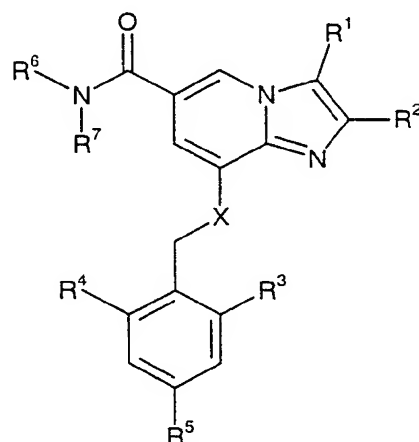
For a review of the pharmacology of the gastric acid pump (the H⁺, K⁺-ATPase), see Sachs
25 et al. (1995) Annu. Rev. Pharmacol. Toxicol. 35: 277-305.

DISCLOSURE OF THE INVENTION

It has surprisingly been found that compounds of the Formula I, which are imidazo
30 pyridine derivatives in which the phenyl moiety is substituted, and in which the imidazo pyridine moiety is substituted with a carboxamide group in 6-position are particularly

effective as inhibitors of the gastrointestinal H^+ , K^+ -ATPase and thereby as inhibitors of gastric acid secretion. The carboxamide group in 6-position is optionally selected to give compounds of Formula I a molecular weight ≤ 600 .

- 5 In one aspect, the invention thus relates to compounds of the general Formula I



I

or a pharmaceutically acceptable salt thereof, wherein

10

R^1 is

- (a) H,
- (b) CH_3 , or
- (c) CH_2OH ;

15

R^2 is

- (a) CH_3 , or
- (b) CH_2CH_3 ;

20

R^3 is

- (a) H,
- (b) C_1 - C_6 alkyl,
- (c) hydroxylated C_1 - C_6 alkyl, or
- (d) halogen;

R⁴ is

- (a) H,
- (b) C₁-C₆ alkyl,
- 5 (c) hydroxylated C₁-C₆ alkyl, or
- (d) halogen;

R⁵ is

- (a) H, or
- 10 (b) halogen;

R⁶ and R⁷ are independently selected substituents, comprising C, H, N, O, S, Se, P and Halogen atoms, which give compounds of Formula I a molecular weight ≤ 600, provided that at least one of R⁶ and R⁷ can not be H, C₁-C₆ alkyl, hydroxylated C₁-C₆ alkyl, or C₁-
15 C₆ alkoxy-substituted C₁-C₆ alkyl, and

X is

- (a) NH, or
- (b) O.

20 As used herein, the term "C₁-C₆ alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said C₁-C₆ alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

25 The term "halogen" includes fluoro, chloro, bromo and iodo.

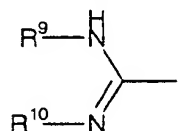
The substituents R⁶ and R⁷ are defined as independently selected substituents, comprising C, H, N, O, S, Se, P or Halogen atoms, which give compounds of Formula I a molecular
30 weight ≤ 600, which is a definition easily understood by a person skilled in the art.

Examples of substituents that fall within the scope of this definition includes, but is not limited to,

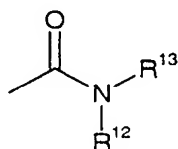
- (a) H,
- (b) C₁-C₆ alkyl,
- 5 (c) hydroxylated C₁-C₆ alkyl,
- (d) C₁-C₆ alkoxy-substituted C₁-C₆ alkyl,
- (e) C₂-C₆ alkenyl,
- (f) C₂-C₆ alkynyl,
- (g) halogenated C₁-C₆ alkyl,
- 10 (h) C₃-C₈ cycloalkyl,
- (i) cycloalkyl-substituted C₁-C₆ alkyl,
- (j) aryl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted by one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, nitro, amino, C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂-N-, or CN or NH₂SO₂,
- 15 (k) aryl substituted C₁-C₆ alkyl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, nitro, amino C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂-N-, CN or NH₂SO₂,
- 20 (l) R⁸-(C₁-C₆) alkyl-, wherein R⁸ is NH₂C=O-, C₁-C₆ alkyl-NHC=O-, (C₁-C₆ alkyl)₂NC=O-, C₁-C₆ alkyl-OOC-, NH₂SO₂-, C₁-C₆ alkyl-SO₂NH-, ArSO₂NH-, cyano, C₁-C₆ alkyl-CO-NH-, C₁-C₆ alkyl-OOCNH-, C₁-C₆ alkyl-O-, C₇-C₁₂ alkyl-O-, C₁-C₆ alkyl-SO-, C₁-C₆ alkyl-S-, C₁-C₆ alkyl-SO₂-, C₁-C₆ alkyl-C=O-, NH₂-, C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂N-, ArCONH-, Ar(C₁-C₆ alkyl)CONH, ArNHSO₂-, (Ar)₂-N-SO₂-, C₁-C₆ alkyl-NHSO₂-, ArS-, ArSO-, ArSO₂-, ArC=O-, NH₂CONH-, C₁-C₆ alkyl-NHCONH-, (C₁-C₆ alkyl)₂-NCONH-, ArNHCONH-, Ar-O-, Ar-NH-, Ar(C₁-C₆ alkyl)N-, (C₁-C₆ alkyl)₂NSO₂-, hydroxylated C₁-C₆ alkyl-O- or morpholinyl; wherein Ar represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, CN, nitro, amino, C₁-C₆ alkyl-NH-, or (C₁-C₆ alkyl)₂N-.
- 30

(m) C₇-C₁₂ ,

(n) OH, O-C₁-C₆ alkyl, or O-hydroxylated C₁-C₆ alkyl,

o)  wherein R⁹ and R¹⁰ are independently H or C₁-C₆ alkyl,

p) R¹¹-(C₁-C₆) alkyl-COO-(C₁-C₆) alkyl- wherein R¹¹ is HOOC-, C₁-C₆ alkyl-
 5 OOC- or an amino carbonyl group with the formula



wherein R¹², R¹³ are the same or different H, or C₁-C₆ alkyl

10 R⁶ and R⁷, together with the nitrogen atom to which they are attached, form a saturated or unsaturated ring optionally containing one or more further heteroatoms (for example morpholine, piperazine, pyrrolidine, piperidine), optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃,
 15 OH, nitro, amino C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂-N-, CN, NH₂SO₂, phenyl, NH₂CO-, C₁-C₆ alkyl-CO-, the ring can be fused with an aromatic ring (such as tetrahydroquinoline);

Both the pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers are within the scope of the invention. It should be understood that all the diastereomeric forms
 20 possible (pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers) are within the scope of the invention. Also included in the invention are derivatives of the compounds of the Formula I which have the biological function of the compounds of the Formula I, such as prodrugs.

25 It will also be appreciated by those skilled in the art, although derivatives of compounds of formula I may not possess pharmacological activity as such, they may be administered parenterally or orally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described

as "prodrugs". All prodrugs of compounds of formula I are included within the scope of the invention.

Depending on the process conditions the end products of the Formula I are obtained either
5 in neutral or salt form. Both the free base and the salts of these end products are within the scope of the invention.

Acid addition salts of the new compounds may in a manner known *per se* be transformed
into the free base using basic agents such as alkali or by ion exchange. The free base
10 obtained may also form salts with organic or inorganic acids.

In the preparation of acid addition salts, preferably such acids are used which form suitably
pharmaceutically acceptable salts. Examples of such acids are hydrohalogen acids such as
hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic
15 or heterocyclic carboxyl or sulphonic acids, such as formic acid, acetic acid, propionic acid,
succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid,
maleic acid, hydroxymaleic acid, pyruvic acid, p-hydroxybenzoic acid, embonic acid,
methanesulphonic acid, ethanesulphonic acid, hydroxyethanesulphonic acid,
halogenbenzenesulphonic acid, toluenesulphonic acid or naphthalenesulphonic acid.

20

Preferred compounds according to the invention are those of the Formula I wherein R¹ is
CH₃ or CH₂OH; R² is CH₃ or CH₂CH₃; R³ is CH₃ or CH₂CH₃; R⁴ is CH₃ or CH₂CH₃;
R⁵ is H, Br, Cl, or F; R⁶ and R⁷ are independently (provided that at least one of R⁶ and R⁷
can not be H, C₁-C₆ alkyl, hydroxylated C₁-C₆ alkyl or C₁-C₆ alkoxy-substituted C₁-C₆
25 alkyl):

- (a) H,
- (b) C₁-C₆ alkyl,
- (c) hydroxylated C₁-C₆ alkyl,
- (d) C₁-C₆ alkoxy-substituted C₁-C₆ alkyl,
- 30 (e) C₂-C₆ alkenyl,
- (f) C₂-C₆ alkynyl,

(g) halogenated C₁-C₆ alkyl,

(h) C₃-C₈ cycloalkyl,

(i) cycloalkyl-substituted C₁-C₆ alkyl,

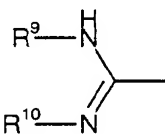
(j) aryl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted by one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, nitro, amino, C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂-N-, or CN or NH₂SO₂,

(k) aryl substituted C₁-C₆ alkyl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, nitro, amino, C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂-N-, CN or NH₂SO₂,

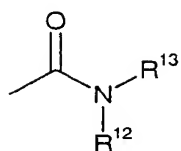
(l) R⁸-(C₁-C₆) alkyl-, wherein R⁸ is NH₂C=O-, C₁-C₆ alkyl-NHC=O-, (C₁-C₆ alkyl)₂NC=O-, C₁-C₆ alkyl-OOC-, NH₂SO₂-, C₁-C₆ alkyl-SO₂NH-, ArSO₂NH-, cyano, C₁-C₆ alkyl-CO-NH-, C₁-C₆ alkyl-OOCNH-, C₁-C₆ alkyl-O-, C₇-C₁₂ alkyl-O-, C₁-C₆ alkyl-SO-, C₁-C₆ alkyl-S-, C₁-C₆ alkyl-SO₂-, C₁-C₆ alkyl-C=O-, NH₂-, C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂N-, ArCONH-, Ar(C₁-C₆ alkyl)CONH-, ArNHSO₂-, (Ar)₂-N-SO₂-, C₁-C₆ alkyl-NHSO₂-, ArS-, ArSO-, ArSO₂-, ArC=O-, NH₂CONH-, C₁-C₆ alkyl-NHCONH-, (C₁-C₆ alkyl)₂-NCONH-, ArNHCONH-, (C₁-C₆ alkyl)₂-N-SO₂-, Ar-O-, Ar-NH-, Ar(C₁-C₆ alkyl)N-, (C₁-C₆ alkyl)₂NSO₂-, hydroxylated C₁-C₆ alkyl-O- or morpholinyl; wherein Ar represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, CN, nitro, amino, C₁-C₆ alkyl-NH-, or (C₁-C₆ alkyl)₂N-,

(m) C₇-C₁₂,

(n) OH, O-C₁-C₆ alkyl, or O-hydroxylated C₁-C₆ alkyl,

(o)  wherein R⁹ and R¹⁰ are independently H or C₁-C₆ alkyl,

(p) R¹¹-(C₁-C₆) alkyl-COO-(C₁-C₆) alkyl- wherein R¹¹ is HOOC-, C₁-C₆ alkyl-OOC- or an amino carbonyl group with the formula



wherein R^{12} , R^{13} are the same or different H, or C_1 - C_6 alkyl

5

R^6 and R^7 , together with the nitrogen atom to which they are attached, form a saturated or unsaturated ring optionally containing one or more further heteroatoms (for example morpholine, piperazine, pyrrolidine, piperidine), optionally substituted with one or more substituents selected from halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, CF_3 ,
 10 OH, nitro, amino C_1 - C_6 alkyl-NH-, $(C_1$ - C_6 alkyl) $_2$ -N-, CN, NH_2SO_2 , phenyl, NH_2CO -, C_1 - C_6 alkyl-CO-, the ring can be fused with an aromatic ring (such as tetrahydroquinoline);

More preferred compounds according to the invention are those of the Formula I wherein
 15 R^1 is CH_3 or CH_2OH ; R^2 is CH_3 , R^3 is CH_3 or CH_2CH_3 ; R^4 is CH_3 or CH_2CH_3 ; R^5 is H, Br, Cl, or F; R^6 and R^7 are independently (provided that at least one of R^6 and R^7 can not be H, C_1 - C_6 alkyl, hydroxylated C_1 - C_6 alkyl or C_1 - C_6 alkoxy-substituted C_1 - C_6 alkyl)

:

- (a) H,
- 20 (b) C_1 - C_6 alkyl,
- (c) hydroxylated C_1 - C_6 alkyl,
- (d) C_1 - C_6 alkoxy-substituted C_1 - C_6 alkyl,
- (e) halogenated C_1 - C_6 alkyl,
- (f) aryl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl,
 25 optionally substituted by one or more substituents selected from halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, CF_3 , OH, C_1 - C_6 alkyl-NH-, $(C_1$ - C_6 alkyl) $_2$ -N-, or CN;
- (g) aryl substituted C_1 - C_6 alkyl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl, optionally substituted with one or more substituents selected from halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, CF_3 , or OH,

- (h) $R^8-(C_1-C_6)$ alkyl-, wherein R^8 is $NH_2C=O-$, C_1-C_6 alkyl- $NHC=O-$, $(C_1-C_6$ alkyl) $_2NC=O-$, C_1-C_6 alkyl- $OOC-$, cyano, C_1-C_6 alkyl- $CO-NH-$, C_1-C_6 alkyl- $OOCNH-$, C_1-C_6 alkyl- $O-$, C_7-C_{12} alkyl- $O-$, C_1-C_6 alkyl- $SO-$, C_1-C_6 alkyl- $S-$, C_1-C_6 alkyl- $C=O-$, $-ArCONH-$, $Ar(C_1-C_6$ alkyl) $CONH$, $ArC=O-$, NH_2CONH- , C_1-C_6 alkyl- $NHCONH-$, $(C_1-C_6$ alkyl) $_2-NCONH-$, $ArNHCONH-$, hydroxylated C_1-C_6 alkyl- $O-$ or morpholinyl; wherein Ar represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl optionally substituted with one or more substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3 , OH, CN,
- (i) C_7-C_{12} alkyl.
- (j) OH,
- (k) $R^{11}-(C_1-C_6)$ alkyl- $COO-(C_1-C_6)$ alkyl- wherein R^{11} is $HOOC-$, or C_1-C_6 alkyl- OOC R^6 and R^7 , together with the nitrogen atom to which they are attached, form a saturated or unsaturated ring optionally containing one or more further heteroatoms (for example morpholine, piperazine, pyrrolidine, piperidine), optionally substituted with one or more substituents selected from halogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, CF_3 , OH, nitro, amino, CN, NH_2SO_2 , phenyl, NH_2CO- , C_1-C_6 alkyl- $CO-$, the ring can be fused with an aromatic ring (such as tetrahydroquinoline)

Most preferred compounds according to the invention are:

- 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-6-(morpholinocarbonyl)-imidazo[1,2-a]pyridine
- N-(4-ethoxyphenyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide
- N-[2-(dimethylamino)-2-oxoethyl]-8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide
- (8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-yl)(4-methylpiperazino)methanone
- 1-((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)-2-(s)-pyrrolidinecarboxamide
- 8-(2-ethyl-6-methylbenzylamino)-N-hydroxy-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide

- (2-ethyl-6-methylbenzylamino)-N-(2-(2-hydroxyethoxy)ethyl)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide
- (8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)(3-hydroxy-1-pyrrolidiny)methanone
- 5 • N-(3,4-dihydroxyphenethyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide
- 8-(2-ethyl-6-methylbenzylamino-3-(hydroxymethyl)-2-methyl-6-(morpholinocarbonyl)-imidazo[1,2-a]pyridine
- N-((8-(2-ethyl-6-methylbenzyl)amino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)guanidine
- 10 • 4-(2-(((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)amino)ethoxy)-4-oxobutanoic acid

Preparation

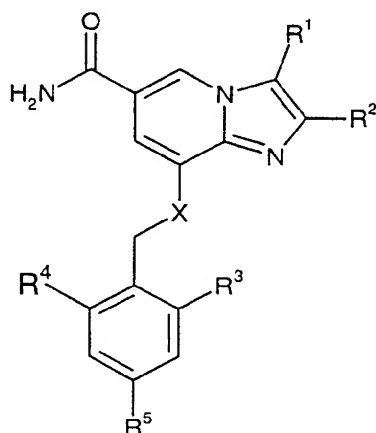
15

The present invention also provides the following process for the manufacture of compounds with the general Formula I.

A process for manufacture of compounds with the general Formula I comprises the following steps:

20

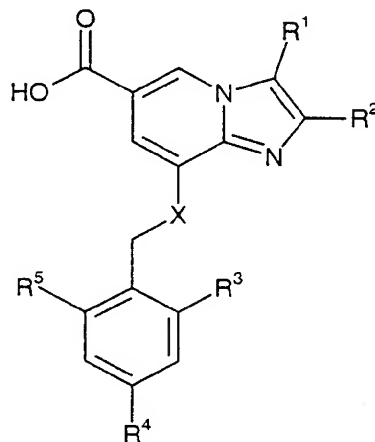
a) Compounds of Formula II



II

wherein R^1 , R^2 , R^3 , R^4 , R^5 , and X are as defined in Formula I, can be hydrolyzed under standard conditions to the corresponding carboxylic acid to the corresponding carboxylic acid compounds of Formula III

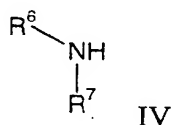
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III

b) Compounds of the Formula III wherein R^1 , R^2 , R^3 , R^4 , R^5 and X is as defined in Formula I can be reacted with amino compounds of Formula IV

10



IV

wherein R^6 and R^7 are as defined for Formula I, in the presence of a coupling reagent to the corresponding amide compounds of the Formula I. The reaction can be carried out in an inert solvent under standard conditions.

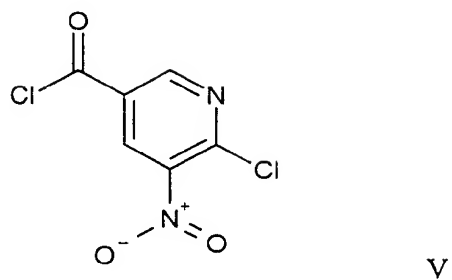
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The present invention also provides the following process for the manufacture of intermediate compounds with the general Formula II.

20

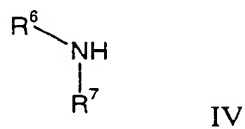
A process for manufacture of compounds with the general Formula II wherein X is NH comprises the following steps:

a) Compounds of the general Formula V

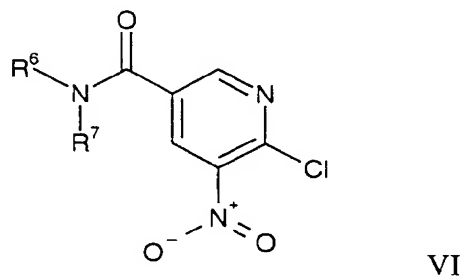


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can be reacted with amino compounds of the general Formula IV

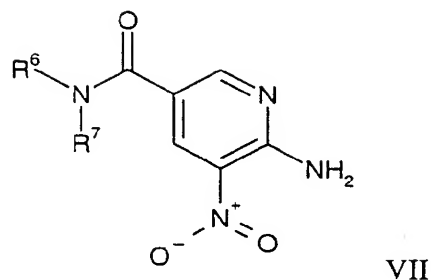


10 wherein R⁶ and R⁷ are both hydrogen, to the corresponding amide of the Formula VI. The reaction can be carried out in standard conditions in an inert solvent.



15 b) Compounds of the general Formula VI can be reacted with ammonia to compounds of the general Formula VII

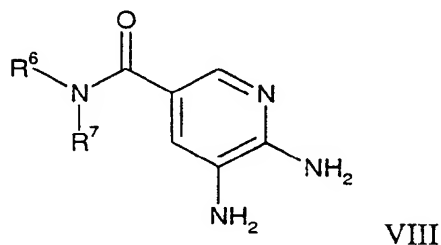
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wherein R^6 and R^7 are both hydrogen. The reactions can be carried out under standard conditions in an inert solvent.

5

c) Compounds of the Formula VII can be reduced e.g. by using hydrogen and a catalyst such as Pd/C to compounds of the Formula VIII

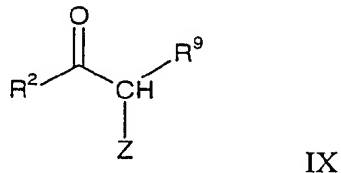


10

wherein R^6 and R^7 are both hydrogen. The reaction can be carried out under standard conditions in an inert solvent.

d) The imidazo[1,2-a]pyridine compounds of the Formula X can be prepared by reacting compounds of the general Formula VIII with compounds of the general Formula IX

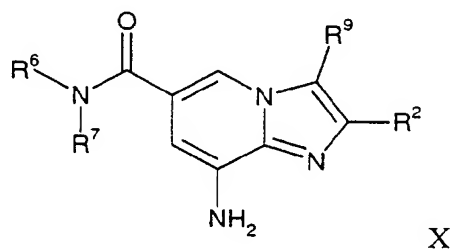
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wherein R^2 is as defined for Formula I and Z is a leaving group such as halogen, mesyl, tosyl and R^9 represents H, CH_3 or an ester group such as $COOCH_3$, $COOC_2H_5$ etc.

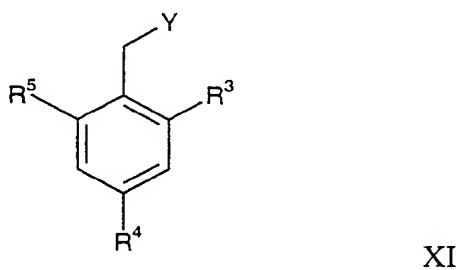
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The reaction is carried out under standard conditions in an inert solvent such as acetone, acetonitrile, alcohol, dimethylformamide, etc. with or without a base.

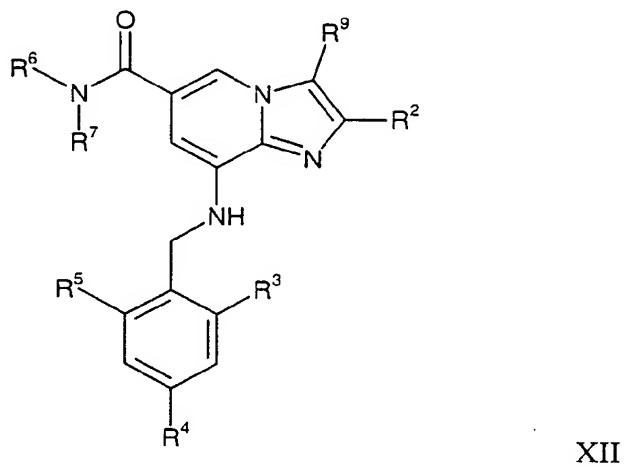


5

e) Compounds of the Formula X can be reacted with compounds of the Formula XI



10 wherein R³, R⁴ and R⁵ are as defined for Formula I and Y is a leaving group, such as a halide, tosyl or mesyl, to the compounds of the Formula XII.



wherein R^2 , R^3 , R^4 , and R^5 are as defined for Formula I and R^6 and R^7 both hydrogen and R^9 is H, CH_3 or an ester group such as $COOCH_3$, $COOC_2H_5$, etc. It is convenient to conduct this reaction in an inert solvent, e.g. acetone, acetonitrile, dimethoxyethane, methanol, ethanol or dimethylformamide with or without a base. The base is e.g. an alkali metal hydroxide, such as sodium hydroxide and potassium hydroxide, an alkali metal carbonate, such as potassium carbonate and sodium carbonate; or an organic amine, such as triethylamine.

f) Reduction of compounds of the general Formula XII wherein R^9 is an ester group e.g. by using lithium borohydride in an inert solvent, such as tetrahydrofuran or diethyl ether, to the compounds of the general Formula I wherein R^1 is CH_2OH and R^6 and R^7 are both hydrogen.

Medical use

15

In a further aspect, the invention relates to compounds of the formula I for use in therapy, in particular for use against gastrointestinal inflammatory diseases. The invention also provides the use of a compound of the formula I in the manufacture of a medicament for the inhibition of gastric acid secretion, or for the treatment of gastrointestinal inflammatory diseases.

20

The compounds according to the invention may thus be used for prevention and treatment of gastrointestinal inflammatory diseases, and gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable, e.g. in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre-and postoperatively to prevent acid aspiration and stress ulceration.

30

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 1000 mg per day of active substance.

5

Pharmaceutical formulations

In yet a further aspect, the invention relates to pharmaceutical compositions containing at least one compound of the invention, or a pharmaceutically acceptable salt thereof, as
10 active ingredient.

The compounds of the invention can also be used in formulations together with other active ingredients, e.g. antibiotics such as amoxicillin.

15 For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. The pharmaceutical formulation contains at least one compound of the invention in combination with one or more pharmaceutically acceptable ingredients. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical
20 preparations are a further object of the invention. Usually the amount of active compounds is between 0.1–95% by weight of the preparation, preferably between 0.1–20% by weight in preparations for parenteral use and preferably between 0.1 and 50% by weight in preparations for oral administration.

25 In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium
30 stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets.

Soft gelatin capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatin capsules. Hard gelatin capsules may contain granules of the active compound.

5 Hard gelatin capsules may also contain the active compound in combination with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Dosage units for rectal administration may be prepared (i) in the form of suppositories
10 which contain the active substance mixed with a neutral fat base; (ii) in the form of a gelatin rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatin rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

15 Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.1% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid
20 preparations may contain coloring agents, flavoring agents, saccharine and carboxymethyl cellulose or other thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

25 Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from 0.1% to 10% by weight. These solutions may also contain stabilizing ingredients and/or buffering ingredients and are dispensed into unit doses in the form of ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to by
30 reconstituted with a suitable solvent extemporaneously before use.

The compounds according to the present invention can also be used in formulations, together or in combination for simultaneous, separate or sequential use, with other active ingredients, *e.g.* for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa. Such other active ingredients may be antimicrobial agents, in particular:

- β -lactam antibiotics such as amoxicillin, ampicillin, cephalothin, cefaclor or cefixime;
- macrolides such as erythromycin, or clarithromycin;
- tetracyclines such as tetracycline or doxycycline;
- aminoglycosides such as gentamycin, kanamycin or amikacin;
- quinolones such as norfloxacin, ciprofloxacin or enoxacin;
- others such as metronidazole, nitrofurantoin or chloramphenicol; or
- preparations containing bismuth salts such as bismuth subcitrate, bismuth subsalicylate, bismuth subcarbonate, bismuth subnitrate or bismuth subgallate.

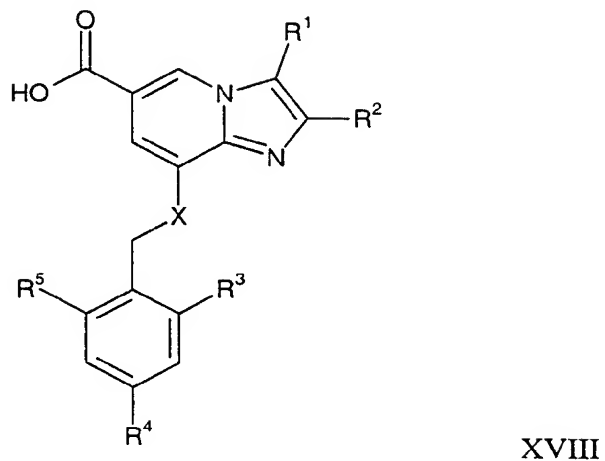
The compounds according to the present invention can also be used together or in combination for simultaneous, separate or sequential use with antacids such as aluminium hydroxide, magnesium carbonate and magnesium hydroxid or alginic acid, or together or in combination for simultaneous, separate or sequential use with pharmaceuticals which inhibit acid secretion, such as, H₂-blockers (*e.g.* cimetidine, ranitidine), H⁺/K⁺ - ATPase inhibitors (*e.g.* omeprazole, pantoprazole, lansoprazole or rabeprazole), or together or in combination for simultaneous, separate or sequential use with gastroprokinetics (*e.g.* cisapride or mosapride).

Intermediates

A further aspect of the invention is new intermediate compounds which are useful in the synthesis of compounds according to the invention.

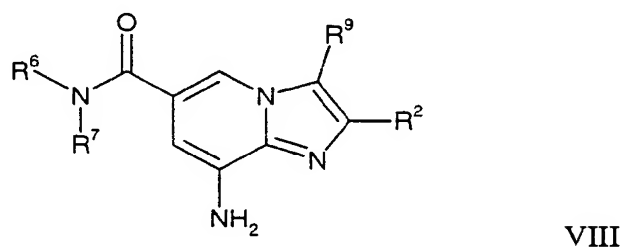
Thus, the invention includes

(a) a compound of the formula XVIII



5 wherein R^1 , R^2 , R^3 , R^4 , R^5 and X are as defined for Formula I.

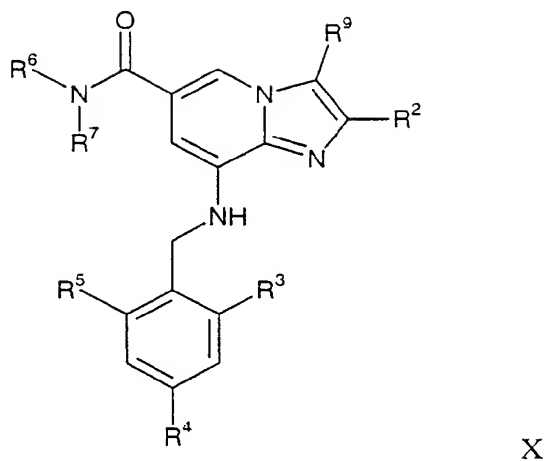
(b) a compound of the formula VIII



10

wherein R^2 , R^6 and R^7 are as defined for Formula I, and R^9 is H, CH^3 or an ester group such as $COOCH_3$, $COOC_2H_5$, etc.;

(c) a compound of the formula X



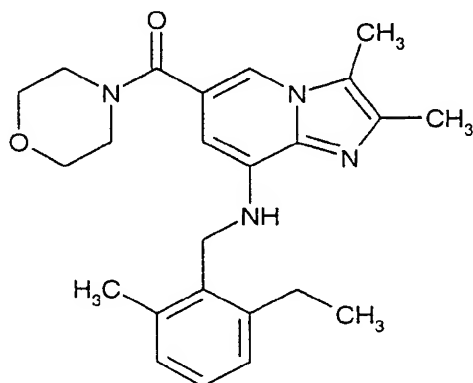
wherein R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for Formula I, and R^9 is an ester group such as COOCH_3 , COOC_2H_5 etc.;

EXAMPLES

1. PREPARATION OF COMPOUNDS OF THE INVENTION

Example 1.1

Synthesis of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-6-(morpholinocarbonyl)-imidazo[1,2-a]pyridine



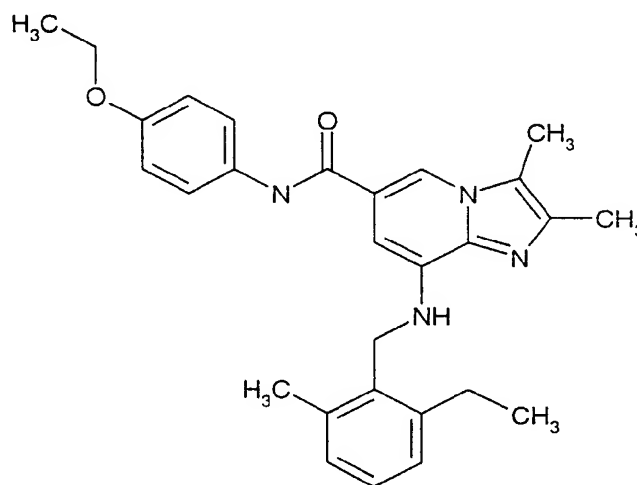
2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.44 mmol) were added to methylene chloride (10 ml).

5 Morpholine (0.12 g, 1.4 mmol) was added and the reaction mixture was stirred at ambient temperature for 1.5 h. The reaction mixture was added to a column with silica gel and purification by chromatography using ethylacetate : methylene chloride (1:1) as eluent gave 0.12 g (66%) of the desired product.

10 ¹H-NMR (300 MHz, CDCl₃): δ 1.2 (t, 3H), 2.32 (s, 3H), 2.35 (s, 3H), 2.37 (s, 3H), 2.7 (q, 2H), 3.7 (s, 8H), 4.35 (d, 2H), 4.95 (bs, 1H), 6.15 (s, 1H), 7.0-7.2 (m, 3H), 7.4 (s, 1H)

Example 1.2

15 *Synthesis of N-(4-ethoxyphenyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide*



20 2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.44 mmol) were added to methylene chloride (10 ml). 4-ethoxyanilin(0.19 g, 1.4 mmol) was added and the reaction mixture was stirred at ambient temperature for 72 h. The solvent was evaporated under reduced pressure and the residue

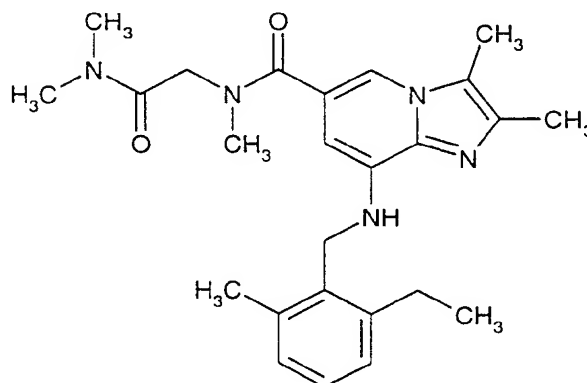
25 was added to a column with silica gel and was purified by chromatography using methylene chloride : methanol (95:5) as eluent. The residue was treated with a hot mixture

of hexane : ethyl acetate (2:1) and the product was filtered off and dried to obtain 0.14 g (74 %) of the desired compound as white crystals.

¹H-NMR (300 MHz, CDCl₃): δ 1.2 (t, 3H), 1.4 (t, 3H), 2.35 (s, 9H), 2.65 (q, 2H), 4.0 (q, 2H), 4.35 (d, 2H), 4.9 (t, 1H), 6.55 (s, 1H), 6.85 (d, 2H), 7.0-7.2 (m, 3H), 7.5 (d, 2H), 7.9 (s, 1H), 8.15 (s, 1H)

Example 1.3

10 *Synthesis of N-[2-(dimethylamine)-2-oxoethyl]-8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide*

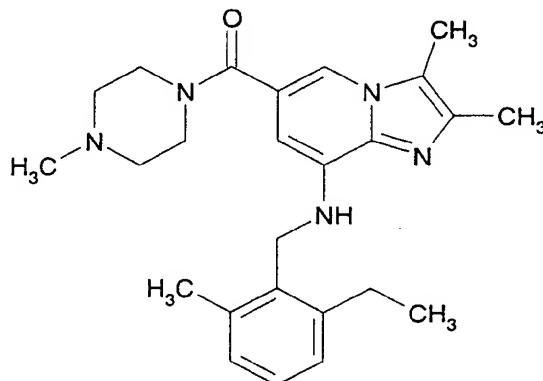


15 2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.13 g, 0.38 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU) (0.12 g, 0.38 mmol) were added to methylene chloride (10 ml). N,N-Dimethyl-2-methylamino-acetamide (0.088 g, 0.38 mmol) was added and the reaction mixture was stirred at ambient temperature for 1 h. The solvent was evaporated under
20 reduced pressure and the residue was purified by column chromatography using methylene chloride : methanol as eluent (95:5) which gave 80 mg (48 %) of the title product.

¹H-NMR (500 MHz, CDCl₃): δ 1.2 (t, 3H), 2.3 (s, 6H), 2.35 (s, 3H), 2.65 (q, 2H), 2.75 (s, 6H), 2.95 (s, 3H), 3.15 (s, 2H), 4.35 (bs, 2H), 4.85 (bs, 1H), 6.25 (s, 1H), 7.0-7.2 (m, 3H),
25 7.45 (s, 1H).

Example 1.4

Synthesis of (8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-yl)(4-methylpiperazino)methanone



5

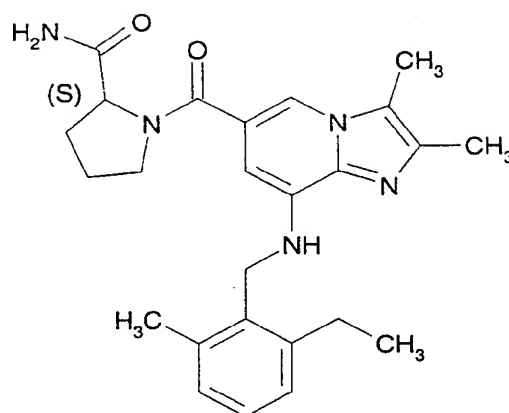
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.5 g, 1.48 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.48 g, 0.15 mmol) were added to methylene chloride (20 ml) and the mixture was stirred for 5 min. N-methylpiperazine (0.16g, 1.6 mmol) was added and the reaction mixture was stirred at ambient temperature overnight. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography on silica gel using methylene chloride:methanol (9:1) as eluent gave 0.46 g (74 %) of the title compound.

¹H-NMR (500 MHz, CDCl₃): δ 1.22 (t, 3H), 2.34 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.47 (bs, 4H), 2.71 (q, 2H), 2.80 (s, 3H), 3.65 (bs, 4H), 4.36 (d, 2H), 4.94 (t, 1H), 6.19 (s, 1H), 7.04-7.18 (m, 3H), 7.42 (s, 1H)

20

Example 1.5

Synthesis of 1-((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)-2-(s)-pyrrolidinecarboxamide

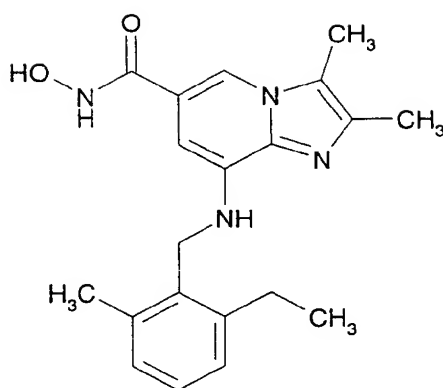


2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol), o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium
 5 tetrafluoroborate (TBTU)(0.14 g, 0.45 mmol) and triethylamine (0.05 g, 0.5 mmol) were added to methylene chloride (10 ml) and the mixture was stirred for 10 min. (S)-prolinamide (0.016 g, 0.45 mmol) was added and the reaction mixture was stirred at ambient temperature for 1 h.. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography on silica gel using methylene
 10 chloride:methanol (9:1) as eluent and crystallization from diethyl ether gave 0.07 g (36 %) of the title compound.

¹H-NMR (500 MHz, CDCl₃): δ 1.21 (t, 3H), 2.1-2.2 (m, 4H), 2.33 (s, 3H), 2.35 (s, 3H),
 2.37 (s, 3H), 2.70 (q, 2H), 3.65-3.75 (m, 2H), 4.36 (d, 2H), 4.80 (bs, 1H), 4.94 (bs, 1H),
 15 5.88 (s, 1H), 6.33 (s, 1H), 6.98 (s, 1H), 7.04-7.19 (m, 3H), 7.54 (s, 1H)

Example 1.6

*Synthesis of 8-(2-ethyl-6-methylbenzylamino)-N-hydroxy-2,3-dimethylimidazo[1,2-
 20 a]pyridine-6-carboxamide*



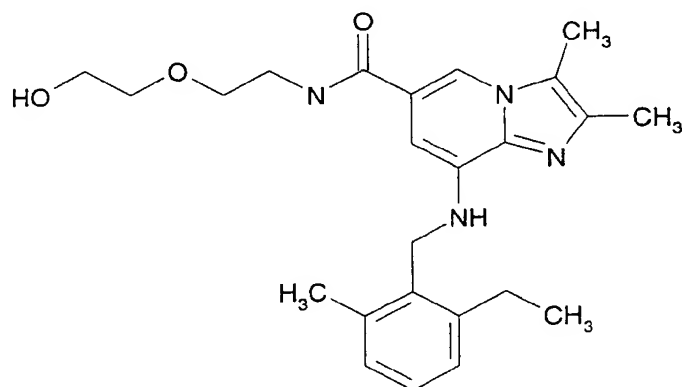
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid
 (0.15 g, 0.45 mmol), o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium
 tetrafluoroborate (TBTU) (0.14 g, 0.45 mmol), triethylamine (0.1 g, 0.99 mmol) and
 5 hydroxylamine hydrochloride (0.031 g, 0.46 mmol) in dimethylformamide (5 ml).

The title compound were prepared according to Example 1.5 (Yield: 0.016 g, 10 %)

10 $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 1.15 (bs, 3H), 2.25 (bs, 9H), 2.6 (bs, 2H), 4.25 (bs, 2H),
 4.95 (bs, 1H), 6.45 (bs, 1H), 6.9-7.1 (m, 3H), 7.75 (bs, 1H)

Example 1.7

15 *Synthesis of (2-ethyl-6-methylbenzylamino)-N-(2-(2-hydroxyethoxy)ethyl)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide*



20 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid
 (0.3 g, 0.88 mmol), o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate

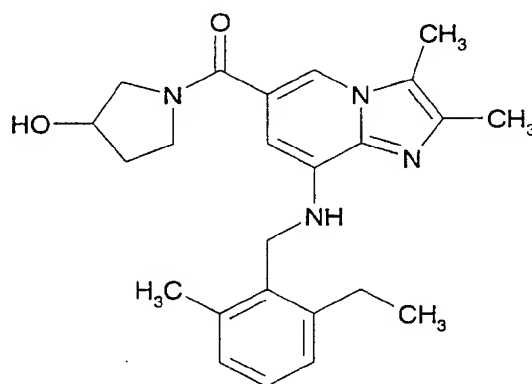
(TBTU)(0.29 g, 0.90 mmol) and 2-(2-aminoethoxy)ethanol (0.2 g, 1.9 mmol) in methylene chloride (10 ml).

The title compound were prepared according to Example 1.5 (Yield: 0.24 g, 80 %)

¹H-NMR (500 MHz,CDCl₃): δ 1.25 (t, 3H), 2.25 (s, 3H), 2.3 (s, 3H), 2.35 (s, 3H), 2.75 (q, 2H), 3.4-3.45 (m, 2H), 3.55-3.7 (m, 6H), 4.35 (d, 2H), 5.05 (t, 1H), 6.45 (s, 1H), 7.0-7.2 (m, 4H), 7.5 (s, 1H)

Example 1.8

Synthesis of (8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)(3-hydroxy-1-pyrrolidinyl)methanone



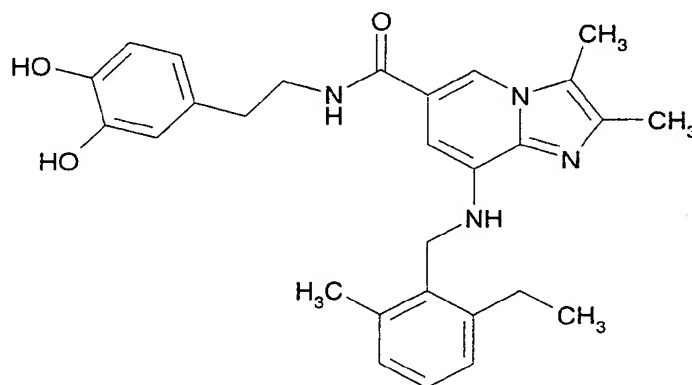
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) , o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.14 g, 0.44 mmol) and 3-pyrrolidinol (0.12 g, 1.4 mmol) in methylene chloride (10 ml).

The title compound were prepared according to Example 1.4. Crystallization from ethylacetate:hexane (2:1) (Yield: 0.24 g, 80 %)

¹H-NMR (300 MHz,CDCl₃): δ 1.23 (t, 3H), 1.93 (bs, 2H), 2.33 (s, 3H), 2.34 (s,3H), 2.41 (s, 3H), 2.70 (q, 2H), 3.51-3.89 (m, 4H), 4.35 (d, 2H), 4.38-4.55 (m, 1H), 5.04 (bs, 1H), 6.35 (s, 1H), 7.01-7.16 (m, 3H), 7.51 (s, 1H)

Example 1.9

Synthesis of *N*-(3,4-dihydroxyphenethyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-*a*]pyridine-6-carboxamide

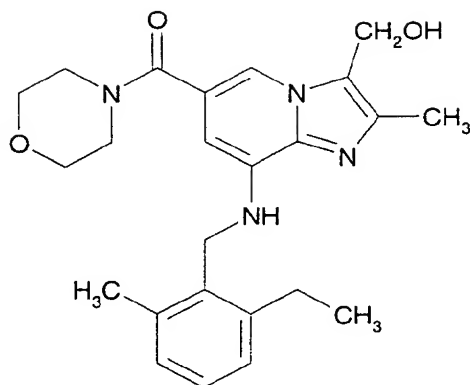


2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-*a*]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) and *o*-Benzotriazol-1-yl-*N,N,N',N'*-Tetramethyluronium tetrafluoroborate (TBTU) (0.14 g, 0.45 mmol) were added to dimethylformamide (10 ml) and the mixture was stirred for 5 min. 3,4-dihydroxyphenethylamin (0.27 g 1.4 mmol) and triethylamine (0.28 g, 1.4 mmol) were added and the reaction mixture was stirred at ambient temperature for 72 h.. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography on silica gel using methylene chloride:methanol (9:1) as eluent and crystallization from acetonitrile gave 0.059 g (28 %) of the title compound.

¹H-NMR (400 MHz, DMSO-*d*₆): δ 1.15 (t, 1H), 2.22 (s, 3H), 2.33 (s, 3H), 2.37 (s, 3H), 2.65-2.74 (m, 4H), 3.41 (q, 2H), 4.37 (d, 2H), 4.85 (t, 1H), 6.48 (dd, 1H), 6.63-6.66 (m, 2H), 6.70 (d, 1H), 7.07-7.21 (m, 3H), 8.04 (d, 1H), 8.49 (t, 1H), 8.63 (s, 1H), 8.75 (s, 1H)

Example 1.10

Synthesis of 8-(2-ethyl-6-methylbenzylamino)-3-(hydroxymethyl)-2-methyl-6-(morpholinocarbonyl)-imidazo[1,2-*a*]pyridine



8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-6-carboxylic acid (0.012 g, 0.034 mmol), o-Benzotriazol-1-yl-N,N,N',N'-
 5 Tetramethyluronium tetrafluoroborate (TBTU) (0.011 g, 0.034 mmol) and morpholine (0.009 g, 0.1 mmol) in methylene chloride (1 ml)

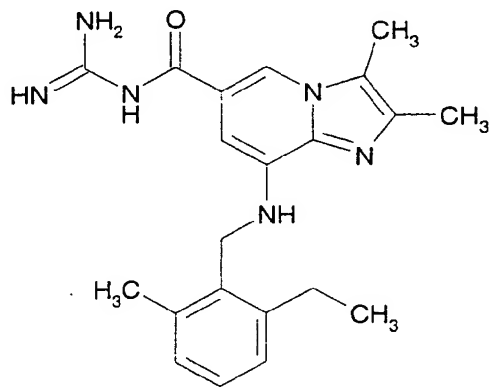
The title compound were prepared according to Example 1.1. (Yield: 0.008 g, 56 %)

10 ¹H-NMR (300 MHz, DMSO-d₆): δ 1.23 (t, 3H), 2.33 (s, 3H), 2.39 (s, 3H), 2.72 (q, 2H), 3.74 (bs, 8H), 4.37 (d, 2H), 4.85 (s, 2H), 5.02 (t, 1H), 6.27 (d, 1H), 7.06-7.22 (m, 3H), 7.75 (d, 1H)

Example 1.86

15

Synthesis of N-((8-(2-ethyl-6-methylbenzyl)amino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)guanidine

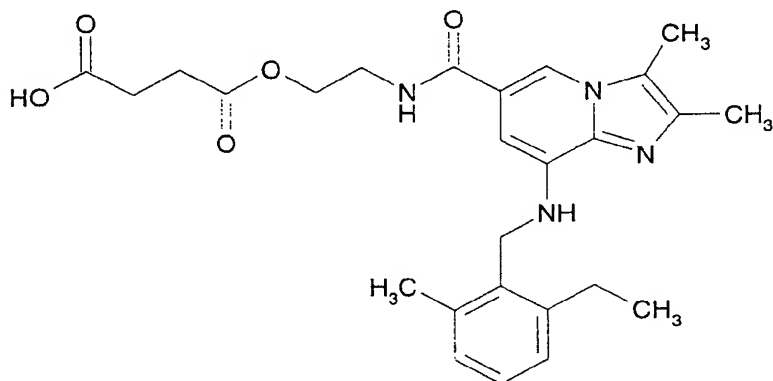


2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.5 g, 1.5 mmol), diisopropylethylamine (0.57 g, 1.5 mmol) and guanidine carbonate (0.53 g, 2.9 mmol) were added to dimethylformamide (10 ml). o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU) (0.48 g, 1.5 mmol) was added and the reaction mixture was stirred at 50 °C for 3 h. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography on silica gel using methylene chloride:methanol (100:15) as eluent and crystallization from diethyl ether gave 0.12 g (21 %) of the title compound.

¹H-NMR (500 MHz, CDCl₃): δ 1.1 (t, 3H), 2.25 (s, 3H), 2.3 (s, 3H), 2.35 (s, 3H), 2.7 (q, 2H), 4.35 (d, 2H), 4.8 (bs, 1H), 6.9 (s, 1H), 7.05-7.2 (m, 3H), 8.25 (s, 1H)

Example 1.87

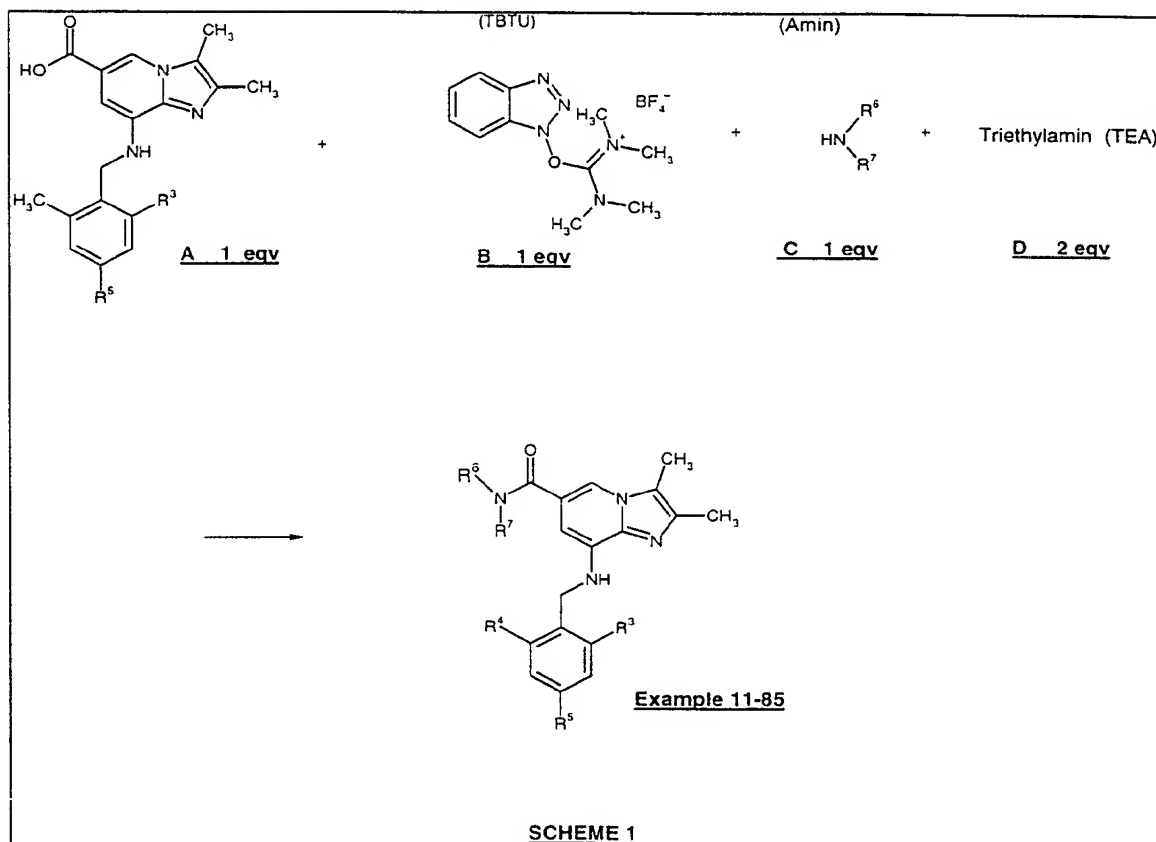
Synthesis of 4-(2-(((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)amino)ethoxy)-4-oxobutanoic acid.



2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide (250 mg, 0.263 mmol) and succinic anhydride (100 mg, 1.00 mmol) were added to 7 ml of acetone. The mixture was refluxed for 48 h. The presipitated product was filtered off and washed with acetone and ether to give 288 mg (91%) of the title compound.

¹H-NMR (500 MHz, DMSO): δ 1.16 (t, 3H), 2.24 (s, 3H), 2.35 (s, 3H), 2.39 (s, 3H), 2.48-2.58 (m, 4H), 2.70 (q, 2H), 3.54 (q, 2H), 4.19 (t, 2H), 4.39 (d, 2H), 4.90 (t, 1H), 6.72 (s, 1H), 7.09-7.22 (m, 3H), 8.08 (s, 1H), 8.59 (t, 1H), 12.25 (s, 1H).

Example 11-85 was prepared by parallel-synthesis using the following method:



5 Solution A : 0.149 mmol in 1 ml dimethylformamide

Solution B (TBTU): 0.297 mmol in 1 ml dimethylformamide

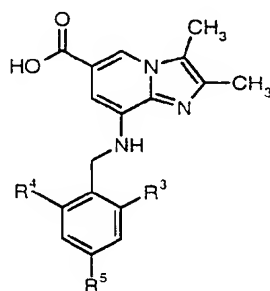
10 Solution C + D: Amin (C) (0.297 mmol in 1 ml dimethylformamide) + TEA (D) (0.594 mmol in 1 ml dimethylamin)

To a solution A (300 μ l) were added solution B (150 μ l) and solution C+D (150 μ l). The reaction was stirred by shaking at room temperature overnight. The solvent was evaporated under reduced pressure. The residue was solved in dichloromethane/methanol (9/1)(600 μ l) and was filtered through a plug of silica gel (100 mg) and the gel was washed with dichloromethane/methanol (9/1) (0.5-1.0 ml). The filtrate was evaporated under reduced pressure to give the desired compounds. (If needed the compounds were purified by preparative HPLC.)

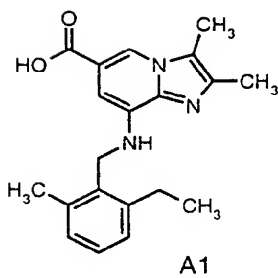
The analyses of the examples was made by HPLC and the compounds were identified by LC-mass spectroscopy. All compounds prepared in Example 11-85 showed a mass spectrum that confirmed the proposed structure.

5

As the starting compound A in the reactions the following compounds were used.

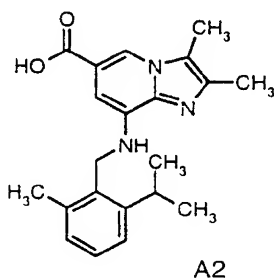


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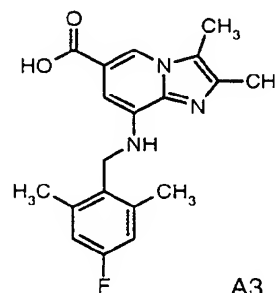


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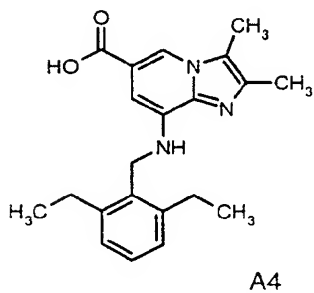
A1



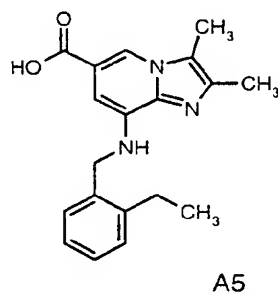
A2



A3



A4

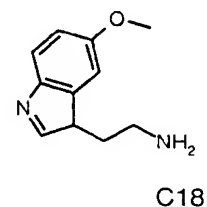
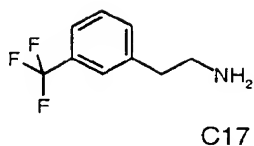
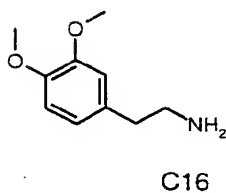
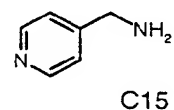
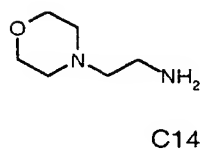
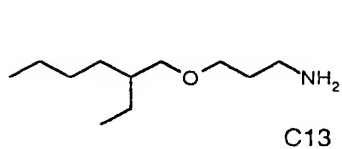
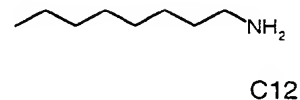
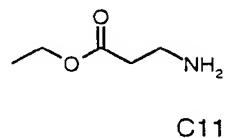
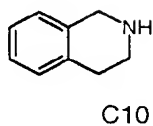
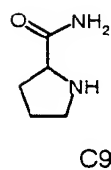
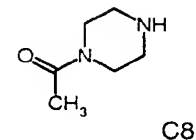
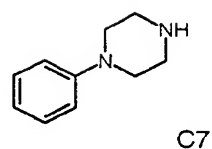
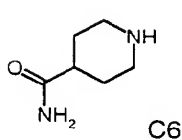
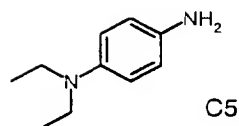
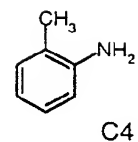
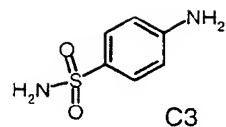
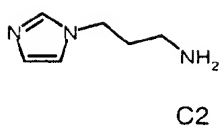
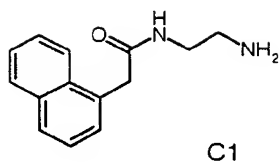
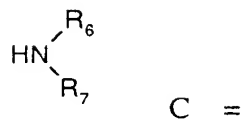


A5

15

As the starting compound C in the reaction the following amines were used.

32

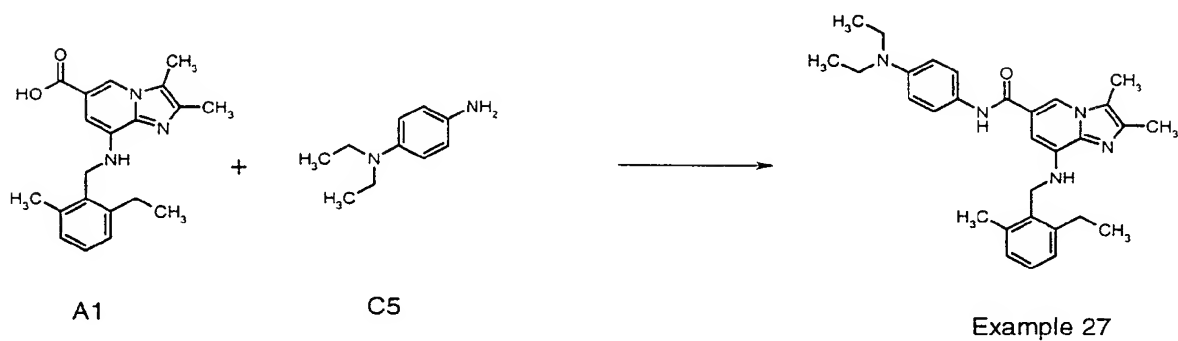


The Examples 11-85 were prepared according to scheme 1

The primary or the secondary amino nitrogen is the nitrogen involved in the reaction.

5

e.g. A1 + C5 \rightarrow Example 27



10

$$A_n + C_n \rightarrow \text{Example 11-85}$$

	A1	A2	A3	A4	A5
C1	Example 11	Example 12	Example 13	Example 14	Example 15
C2	Example 16	Example 17	Example 18	Example 19	Example 20
C3	-	-	-	-	Example 21
C4	Example 22	Example 23	Example 24	Example 25	Example 26
C5	Example 27	Example 28	Example 29	Example 30	Example 31
C6	Example 32	Example 33	Example 34	Example 35	Example 36
C8	Example 37	Example 38	Example 39	Example 40	Example 41
C9	Example 42	Example 43	Example 44	Example 45	Example 46
C10	Example 47	Example 48	Example 49	Example 50	Example 51
C11	-	Example 52	Example 53	Example 54	Example 55
C12	-	Example 56	Example 57	Example 58	Example 59
C13	-	Example 60	Example 61	Example 62	Example 63
C14	-	-	Example 64	Example 65	Example 66
C15	Example 67	Example 68	Example 69	Example 70	Example 71
C16	-	Example 72	Example 73	Example 74	Example 75
C17	Example 76	Example 77	Example 78	Example 79	Example 80
C18	Example 81	Example 82	Example 83	Example 84	Example 85

5 2. PREPARATION OF INTERMEDIATES

Example 2.1

Synthesis of 8-(2-ethylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid

10

8-(2-ethylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide (1.0 g, 0.0031 mol) and sodium hydroxide (1.2 g, 0.031 mol) were solved in ethanol (95 %)(30 ml) and

was refluxed overnight. The solvent was evaporated under reduced pressure and to the residue was added water. The pH was adjusted to 7 by addition of conc HCl (2.6 ml) and the solid that precipitated was isolated by filtration, washed with water and dried to give 1.0 g (99 %) of the title compound.

5

¹H-NMR (300 MHz, DMSO-d₆): δ 1.2 (t, 3H), 2.25 (s, 3H), 2.35 (s, 3H), 2.7 (q, 2H), 4.45 (d, 2H), 6.3 (s, 1H), 6.45 (t, 1H), 7.05-7.25 (m, 4H), 7.95 (s, 1H)

Example 2.2

10

Synthesis of 8-(2,6-diethylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid

8-(2,6-diethylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide (1.5 g, 0.0043 mol) and sodium hydroxide (1.7 g, 0.043 mol) were solved in ethanol (95 %) (30 ml).

15

The title compound were prepared according to Example 1.4. (Yield: 1.5 g, 99 %)

¹H-NMR (400 MHz, DMSO-d₆): δ 1.14 (t, 6H), 2.22 (s, 3H), 2.37 (s, 3H), 2.67 (q, 4H), 4.37 (d, 2H), 4.89 (t, 1H), 6.68 (s, 1H), 7.11 (d, 2H), 7.23 (t, 1H), 8.09 (s, 1H)

20

Example 2.3

Synthesis of 8-(2,6-dimethyl-4-fluorobenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid

25

8-(2,6-dimethyl-4-fluorobenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (1.47 g, 0.0034 mol) and sodium hydroxide (1.7 g, 0.034 mol) were solved in ethanol (95 %) (30 ml).

The title compound were prepared according to Example 2.1. (Yield: 1.1 g, 95 %)

30

¹H-NMR (400 MHz, DMSO-d₆): δ 2.23 (s, 3H), 2.34 (s, 6H), 2.36 (s, 3H), 4.31 (d, 2H), 5.04 (bs, 1H), 6.70 (s, 1H), 6.90 (d, 2H), 8.02 (s, 1H)

Example 2.4

5

Synthesis of 8-(2-isopropyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid

8-(2-isopropyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (1.2 g, 0.0027 mol) and sodium hydroxide (1.1 g, 0.027 mol) were solved in ethanol(95 %) (25 ml).

The title compound were prepared according to Example 2.1. (Yield: 1.1 g, 95 %)

¹H-NMR (300 MHz, DMSO-d₆): δ 1.69 (d, 6H), 2.74 (s, 3H), 2.85 (s, 3H), 2.89 (s, 3H), 3.73 (m, 1H), 4.90 (d, 2H), 5.48 (t, 1H), 7.19 (s, 1H), 7.55-7.61 (m, 1H), 7.70-7.76 (m, 2H), 8.60 (s, 1H)

15

Example 2.5

Synthesis of 8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylic acid

20

8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (11.0 g, 0.025 mol) and sodium hydroxide (7.0 g, 0.17 mol) were solved in ethanol(95 %) (120 ml) and was refluxed for 20 h. The solvent was evaporated under reduced pressure and to the residue was added water (150 ml). The pH was adjusted to 5 by addition of conc HCl and acetic acid and the solid that precipitated was isolated by filtration. washed with water and acetone, and dried to give 7.6 g (88 %) of the title compound

25

30

¹H-NMR (500 MHz.DMSO-d₆): δ 1.15 (t, 3H), 2.26 (s, 3H), 2.34 (s, 3H), 2.39 (s, 3H), 2.69 (q, 2H), 4.38 (d, 2H), 5.2 (bs, 1H), 6.73 (s, 1H), 7.07-7.2 (m, 3H), 8.12 (s, 1H)

Example 2.6

5

Synthesis of 8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-6-carboxylic acid

8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-6-carboxamide (0.02 g, 0.057 m mol) and sodium hydroxide (0.02 g, 0.29 mmol) were solved
10 in ethanol (95 %) (1 ml) and was refluxed for 20 h. The solvent was evaporated under reduced pressure and to the residue was added water (1 ml). The pH was adjusted to 5 by addition of acetic acid and the solid that precipitated was isolated by filtration. washed with water and dried to give 0.012 g (60 %) of the title compound.

15

¹H-NMR (300 MHz.DMSO-d₆): δ 1.14 (t, 3H), 2.22 (s, 3H), 2.33 (s, 3H), 2.67 (q, 2H), 4.33 (d, 2H), 4.55 (bs, 1H), 4.67 (s, 2H), 6.83 (s, 1H), 7.06-7.24 (m, 3H), 8.15 (s, 1H)

BIOLOGICAL TESTS

20

1. In vitro experiments

Acid secretion inhibition in isolated rabbit gastric glands

25 Inhibiting effect on acid secretion *in vitro* in isolated rabbit gastric glands was measured as described by Berglindh et al. (1976) Acta Physiol. Scand. 97, 401-414.

Determination of H⁺,K⁺-ATPase activity

30 Membrane vesicles (2.5 to 5 µg) were incubated for 15 min at +37°C in 18 mM Pipes/Tris buffer pH 7.4 containing 2 mM MgCl₂, 10 mM KCl and 2 mM ATP. The ATPase activity

was estimated as release of inorganic phosphate from ATP, as described by LeBel et al. (1978) Anal. Biochem. 85, 86-89.

2. *In vivo experiments*

5

Inhibiting effect on acid secretion in female rats

Female rats of the Sprague-Dawley strain are used. They are equipped with cannulated fistulae in the stomach (lumen) and the upper part of the duodenum, for collection of
10 gastric secretions and administration of test substances, respectively. A recovery period of 14 days after surgery is allowed before testing commenced.

Before secretory tests, the animals are deprived of food but not water for 20 h. The stomach is repeatedly washed through the gastric cannula with tap water (+37°C), and 6 ml Ringer-
15 Glucose given subcutaneously. Acid secretion is stimulated with infusion during 2.5-4 h (1.2 ml/h, subcutaneously) of pentagastrin and carbachol (20 and 110 nmol/kg·h, respectively), during which time gastric secretions are collected in 30-min fractions. Test substances or vehicle are given either at 60 min after starting the stimulation (intravenous and intraduodenal dosing, 1 ml/kg), or 2 h before starting the stimulation (oral dosing, 5
20 ml/kg, gastric cannula closed). The time interval between dosing and stimulation may be increased in order to study the duration of action. Gastric juice samples are titrated to pH 7.0 with NaOH, 0.1 M, and acid output calculated as the product of titrant volume and concentration.

25 Further calculations are based on group mean responses from 4-6 rats. In the case of administration during stimulation; the acid output during the periods after administration of test substance or vehicle are expressed as fractional responses, setting the acid output in the 30-min period preceding administration to 1.0. Percentage inhibition is calculated from the fractional responses elicited by test compound and vehicle. In the case of administration
30 before stimulation; percentage inhibition is calculated directly from acid output recorded after test compound and vehicle.

Bioavailability in rat

Adult rats of the Sprague-Dawley strain are used. One to three days prior to the
5 experiments all rats are prepared by cannulation of the left carotid artery under anaesthesia.
The rats used for intravenous experiments are also cannulated in the jugular vein (Popovic
(1960) J. Appl. Physiol. 15, 727-728). The cannulas are exteriorized at the nape of the
neck.

10 Blood samples (0.1 - 0.4 g) are drawn repeatedly from the carotid artery at intervals up to
5.5 hours after given dose. The samples are frozen until analysis of the test compound.

Bioavailability is assessed by calculating the quotient between the area under blood/plasma
concentration (AUC) curve following (i) intraduodenal (i.d.) or oral (p.o.) administration
15 and (ii) intravenous (i.v.) administration from the rat or the dog, respectively.

The area under the blood concentration vs. time curve, AUC, is determined by the
log/linear trapezoidal rule and extrapolated to infinity by dividing the last determined blood
concentration by the elimination rate constant in the terminal phase. The systemic
20 bioavailability (F%) following intraduodenal or oral administration is calculated as
$$F(\%) = (AUC \text{ (p.o. or i.d.)} / AUC \text{ (i.v.)}) \times 100.$$

Inhibition of gastric acid secretion and bioavailability in the conscious dog.

25 Labrador retriever or Harrier dogs of either sex are used. They are equipped with a
duodenal fistula for the administration of test compounds or vehicle and a cannulated
gastric fistula or a Heidenhaim-pouch for the collection of gastric secretion.

Before secretory tests the animals are fasted for about 18 h but water is freely allowed.
30 Gastric acid secretion is stimulated for up to 6.5 h infusion of histamine dihydrochloride
(12 ml/h) at a dose producing about 80% of the individual maximal secretory response, and

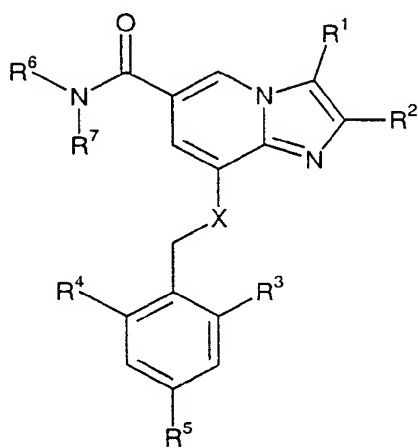
gastric juice collected in consecutive 30-min fractions. Test substance or vehicle is given orally, i.d. or i.v., 1 or 1.5 h after starting the histamine infusion, in a volume of 0.5 ml/kg body weight. In the case of oral administration, it should be pointed out that the test compound is administered to the acid secreting main stomach of the Heidenham-pouch dog.

The acidity of the gastric juice samples are determined by titration to pH 7.0, and the acid output calculated. The acid output in the collection periods after administration of test substance or vehicle are expressed as fractional responses, setting the acid output in the fraction preceding administration to 1.0. Percentage inhibition is calculated from fractional responses elicited by test compound and vehicle.

Blood samples for the analysis of test compound concentration in plasma are taken at intervals up to 4 h after dosing. Plasma is separated and frozen within 30 min after collection and later analyzed. The systemic bioavailability (F%) after oral or i.d. administration is calculated as described above in the rat model.

CLAIMS

1. A compound of the formula I



I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is

- 10 (a) H,
(b) CH_3 , or
(c) CH_2OH ;

R^2 is

- 15 (a) CH_3 , or
(b) CH_2CH_3 ;

R^3 is

- 20 (a) H,
(b) C_1 - C_6 alkyl,
(c) hydroxylated C_1 - C_6 alkyl, or
(d) halogen;

R^4 is

- 25 (a) H,

- (b) C₁-C₆ alkyl,
- (c) hydroxylated C₁-C₆ alkyl, or
- (d) halogen;

5 R⁵ is

- (a) H, or
- (b) halogen;

R⁶ and R⁷ are independently selected substituents, comprising C, H, N, O, S, Se, P or
10 Halogen atoms, which give compounds of Formula I a molecular weight ≤ 600, provided
that at least one of R⁶ and R⁷ can not be H, C₁-C₆ alkyl, hydroxylated C₁-C₆ alkyl, or C₁-
C₆ alkoxy-substituted C₁-C₆ alkyl, and

X is

- 15
- (a) NH, or
 - (b) O.

2. A compound according to formula I wherein R¹ is CH₃ or CH₂OH; R² is CH₃ or
CH₂CH₃; R³ is CH₃ or CH₂CH₃; R⁴ is CH₃ or CH₂CH₃; R⁵ is H, Br, Cl, or F; R⁶ and R⁷
20 are independently (provided that at least one of R⁶ and R⁷ can not be H, C₁-C₆ alkyl,
hydroxylated C₁-C₆ alkyl or C₁-C₆ alkoxy-substituted C₁-C₆ alkyl)

:

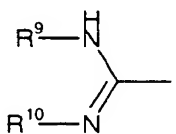
- (a) H,
- (b) C₁-C₆ alkyl,
- 25 (c) hydroxylated C₁-C₆ alkyl,
- (d) C₁-C₆ alkoxy-substituted C₁-C₆ alkyl,
- (e) C₂-C₆ alkenyl,
- (f) C₂-C₆ alkynyl,
- (g) halogenated C₁-C₆ alkyl,
- 30 (h) C₃-C₈ cycloalkyl.
- (i) cycloalkyl-substituted C₁-C₆ alkyl.

(j) aryl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted by one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, nitro, amino, C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂-N-, or CN or NH₂SO₂,

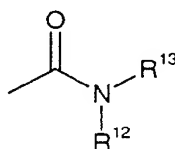
5 (k) aryl substituted C₁-C₆ alkyl, in which aryl represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, nitro, amino C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂-N-, CN or NH₂SO₂,

(l) R⁸-(C₁-C₆) alkyl-, wherein R⁸ is NH₂C=O-, C₁-C₆ alkyl-NHC=O-, (C₁-C₆ alkyl)₂NC=O-, C₁-C₆ alkyl-OOC-, NH₂SO₂-, C₁-C₆ alkyl-SO₂NH-,
 10 ArSO₂NH-, cyano, C₁-C₆ alkyl-CO-NH-, C₁-C₆ alkyl-OOCNH-, C₁-C₆ alkyl-O-, C₇-C₁₂ alkyl-O-, C₁-C₆ alkyl-SO-, C₁-C₆ alkyl-S-, C₁-C₆ alkyl-SO₂-, C₁-C₆ alkyl-C=O-, NH₂-, C₁-C₆ alkyl-NH-, (C₁-C₆ alkyl)₂N-, ArCONH-, Ar(C₁-C₆ alkyl)CONH-, ArNHSO₂-, (Ar)₂-N-SO₂-, C₁-C₆ alkyl-NHSO₂-, ArS-, ArSO-,
 15 ArSO₂-, ArC=O-, NH₂CONH-, C₁-C₆ alkyl-NHCONH-, (C₁-C₆ alkyl)₂-NCONH-, ArNHCONH-, (C₁-C₆ alkyl)₂-N-SO₂-, Ar-O-, Ar-NH-, Ar(C₁-C₆ alkyl)N-, hydroxylated C₁-C₆ alkyl-O- or morpholinyl; wherein Ar represents phenyl, pyridyl, thienyl, imidazolyl, indolyl, naphthyl or furanyl, optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, CN, nitro, amino, C₁-C₆ alkyl-NH-, or (C₁-C₆ alkyl)₂N-,
 20 (m) C₇-C₁₂,

(n) OH, O-C₁-C₆ alkyl, or O-hydroxylated C₁-C₆ alkyl,

(o)  wherein R⁹ and R¹⁰ are independently H or C₁-C₆ alkyl,

(p) R¹¹-(C₁-C₆) alkyl-COO-(C₁-C₆) alkyl- wherein R¹¹ is HOOC-, C₁-C₆ alkyl-OOC- or an amino carbonyl group with the formula



wherein R^{12} , R^{13} are the same or different H, or C_1 - C_6 alkyl

R^6 and R^7 , together with the nitrogen atom to which they are attached, form a
 5 saturated or unsaturated ring optionally containing one or more further heteroatoms (for
 example morpholine, piperazine, pyrrolidine, piperidine), optionally substituted with one or
 more substituents selected from halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, CF_3 , OH, nitro,
 amino C_1 - C_6 alkyl-NH-, (C_1 - C_6 alkyl) $_2$ -N-, CN, NH_2SO_2 , phenyl, NH_2CO -, C_1 - C_6
 alkyl-CO-, the ring can be fused with an aromatic ring (such as tetrahydroquinoline),
 10 or a pharmaceutically acceptable salt thereof.

3. A compound according to claim 1 or 2 I wherein R^1 is CH_3 or CH_2OH ; R^2 is CH_3 , R^3 is
 CH_3 or CH_2CH_3 ; R^4 is CH_3 or CH_2CH_3 ; R^5 is H, Br, Cl, or F; R^6 and R^7 are
 independently (provided that at least one of R^6 and R^7 can not be H, C_1 - C_6 alkyl,
 15 hydroxylated C_1 - C_6 alkyl or C_1 - C_6 alkoxy-substituted C_1 - C_6 alkyl),
 (a) H,
 (b) C_1 - C_6 alkyl,
 (c) hydroxylated C_1 - C_6 alkyl.
 (d) C_1 - C_6 alkoxy-substituted C_1 - C_6 alkyl,
 20 (e) halogenated C_1 - C_6 alkyl,
 (f) aryl, in which aryl represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl,
 optionally substituted by one or more substituents selected from halogen, C_1 - C_6 alkyl,
 C_1 - C_6 alkoxy, CF_3 , OH, C_1 - C_6 alkyl-NH-, (C_1 - C_6 alkyl) $_2$ -N-, or CN;
 (g) aryl substituted C_1 - C_6 alkyl, in which aryl represents phenyl, pyridyl, imidazolyl,
 25 indolyl, or naphthyl, optionally substituted with one or more substituents selected from
 halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, CF_3 , or OH,
 (h) R^8 -(C_1 - C_6) alkyl-, wherein R^8 is $NH_2C=O$ -, C_1 - C_6 alkyl-NHC=O-, (C_1 - C_6
 alkyl) $_2$ NC=O-, C_1 - C_6 alkyl-OOC-, cyano, C_1 - C_6 alkyl-CO-NH-, C_1 - C_6 alkyl-
 OOCNH-, C_1 - C_6 alkyl-O-, C_7 - C_{12} alkyl-O-, C_1 - C_6 alkyl-SO-, C_1 - C_6 alkyl-S-,
 30 C_1 - C_6 alkyl-C=O-, ArCONH-, Ar(C_1 - C_6 alkyl)CONH, ArC=O-, NH_2CONH - C_1 -
 C_6 alkyl-NHCONH-, (C_1 - C_6 alkyl) $_2$ -NCONH-, ArNHCONH-, hydroxylated C_1 - C_6

alkyl-O- or morpholinyl ; wherein Ar represents phenyl, pyridyl, imidazolyl, indolyl, or naphthyl optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, CN,

(i) C₇-C₁₂ alkyl.

5 (j) OH ,

(k) R¹¹-(C₁-C₆) alkyl-COO-(C₁-C₆) alkyl- wherein R¹¹ is HOOC-, or C₁-C₆ alkyl - OOC₂

—R⁶ and R⁷, together with the nitrogen atom to which they are attached, form a saturated or unsaturated ring optionally containing one or more further heteroatoms (for example
10 morpholine, piperazine, pyrrolidine, piperidine), optionally substituted with one or more substituents selected from halogen, C₁-C₆ alkyl, C₁-C₆ alkoxy, CF₃, OH, nitro, amino, CN, NH₂SO₂, phenyl, NH₂CO-, C₁-C₆ alkyl-CO-, the ring can be fused with an aromatic ring (such as tetrahydroquinoline)

15 4. The compound according to claims 1 to 3 being;

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-6-(morpholinocarbonyl)-imidazo[1,2-a]pyridine,

N-(4-ethoxyphenyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide,

20 N-[2-(dimethylamine)-2-oxoethyl]-8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide,

(8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-yl)(4-methylpiperazino)methanone,

1-((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)-2-(s)-pyrrolidinecarboxamide,

8-(2-ethyl-6-methylbenzylamino)-N-hydroxy-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide,

(2-ethyl-6 methylbenzylamino)-N-(2-(2-hydroxyethoxy)ethyl)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide,

30 (8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)(3-

hydroxy-1-pyrrolidiny)methanone,

N-(3,4-dihydroxyphenethyl)-8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide,

8-(2-ethyl-6-methylbenzylamino-3-(hydroxymethyl)-2-methyl-6-(morpholinocarbonyl)-imidazo[1,2-a]pyridine,

N-((8-(2-ethyl-6-methylbenzyl)amino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)guanidine,

4-(2-(((8-(2-ethyl-6-methylbenzylamino)-2,3-dimethylimidazo[1,2-a]pyridin-6-yl)carbonyl)amino)ethoxy)-4-oxobutanoic acid,

or a pharmaceutically acceptable salt thereof.

5. A compound according to any of claims 1-4 as a hydrochloride or mesylate salt.

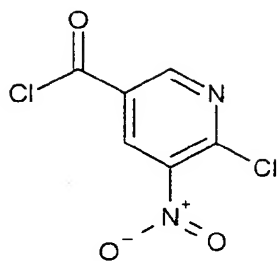
6. Products containing a compound according to any of claims 1-5 and at least one antimicrobial agent as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of gastrointestinal inflammatory diseases.

7. Products containing a compound according to any of claims 1-5 and at least one proton pump inhibitor as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of gastrointestinal inflammatory diseases.

8. A process for the preparation of a compound according to any one of claims 1 to 5, wherein X is NH, comprising

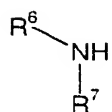
(a) reacting a compound of the Formula II

47



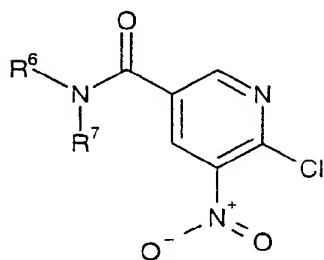
II

with a compound of the Formula III



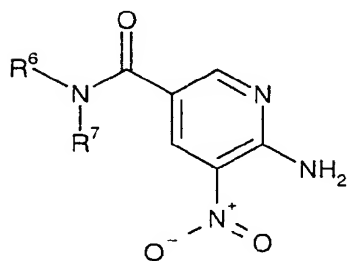
III

wherein R^6 and R^7 are as defined in claim 1, in an inert solvent, to a compound of the Formula IV,



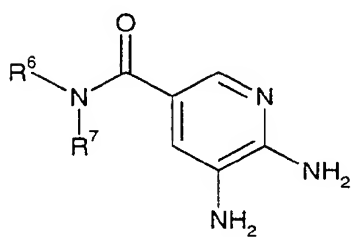
IV

(b) reacting a compound of the Formula IV wherein R^6 and R^7 are as defined in claim 1, with ammonia in an inert solvent to a compound of the Formula V



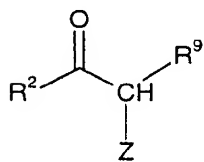
V

(c) reducing a compound of the Formula V wherein R^6 and R^7 are as defined in claim 1 in an inert solvent under standard conditions to a compound of the Formula VI



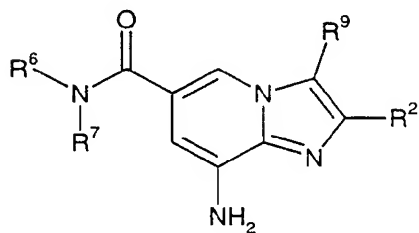
VI

(d) reacting a compound of the Formula VI wherein R^6 and R^7 are as defined in claim 1 with a compound of Formula VII



VII

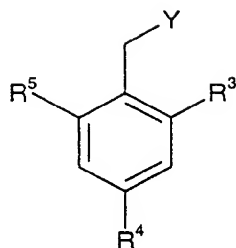
wherein R^2 is as defined in claim 1, Z is a leaving group and R^9 represent H, CH_3 or an ester group, in an inert solvent with or without a base to a compound of the Formula VIII



VIII

(e) reacting a compound of the Formula VIII wherein R^6 , R^7 and R^2 are as defined in claim 1, and R^9 is H, CH_3 or an ester group with a compound of Formula IX

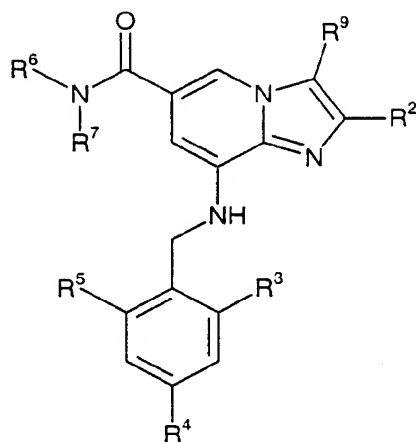
49



IX

wherein R^3 , R^4 , and R^5 are as defined in claim 1, and Y is a leaving group in an inert solvent with or without a base, to a compound of the Formula X

5



X

(f) reducing a compound of Formula X wherein R^9 is an ester group in an inert solvent to a compound of the Formula I wherein R^1 is CH_2OH and X is NH.

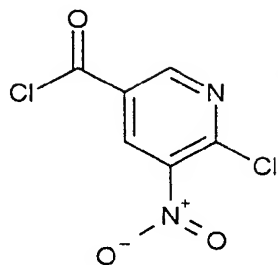
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9. A process for the preparation of a compound according to any one of claims 1 to 5, wherein X is NH and R^1 is H or CH_3 , comprising

(a) reacting a compound of the Formula II

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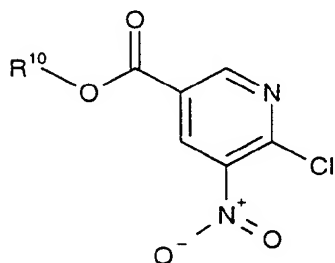
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II

with an alcohol compound of the general formula R^{10} -OH, wherein R^{10} is an alkyl group under standard conditions, to a compound of the Formula XI

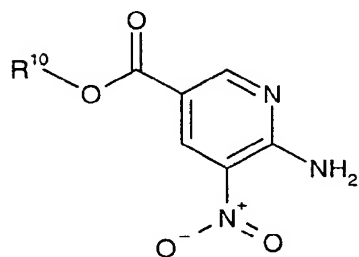
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XI

(b) reacting a compound of the Formula XI wherein R^{10} is an alkyl group, with ammonia in an inert solvent under standard conditions to a compound of the Formula XII

10

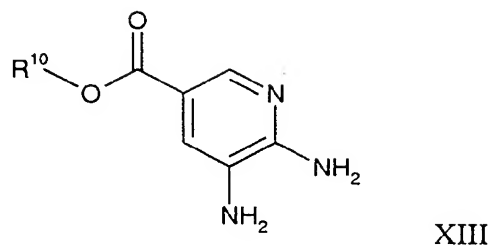


XII

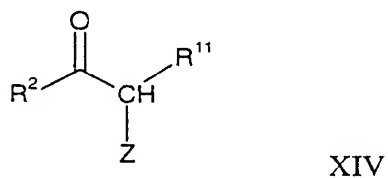
(c) reducing a compound of the Formula XII wherein R^{10} is an alkyl group in an inert solvent under standard conditions to a compound of the Formula XIII

15

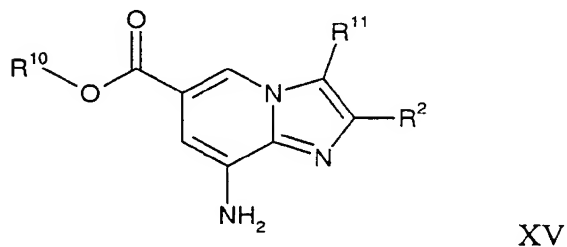
51



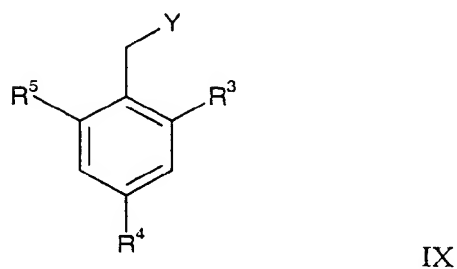
(d) reacting a compound of the Formula XIII wherein R^{10} is an alkyl group with a compound of Formula XIV



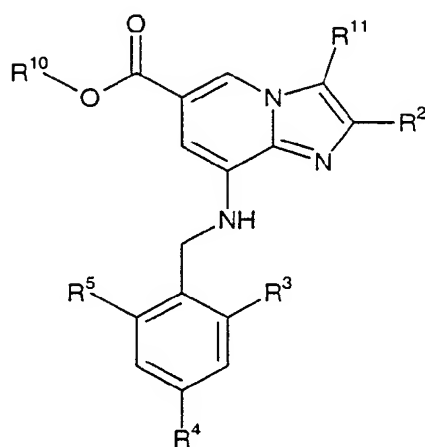
wherein R^2 is as defined in claim 1, Z is a leaving group and R^{11} represent H or CH_3 , in an inert solvent with or without a base to a compound of the Formula XV



(e) reacting a compound of the Formula XV wherein R^{10} is an alkyl group, R^2 are as defined in claim 1 and R^{11} is H or CH_3 with a compound of Formula IX

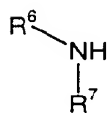


wherein R^3 , R^4 , and R^5 are as defined in claim 1 and Y is a leaving group in an inert solvent with or without a base to a compound of the Formula XVI



XVI

(f) reacting a compound of Formula XVI wherein R^2 , R^3 , R^4 and R^5 are as defined in claim 1, R^{10} is an alkyl group and R^{11} is H or CH_3 with a compound of Formula III



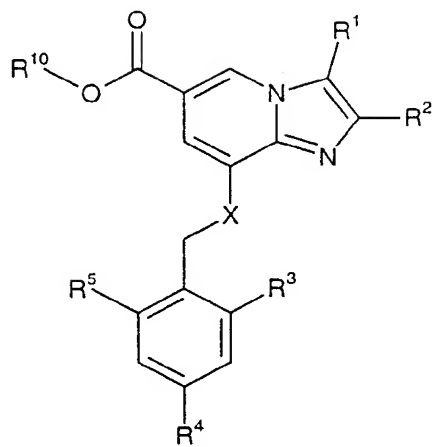
III

wherein R^6 and R^7 are as defined in claim 1, under standard conditions, to a compound of Formula I wherein R^1 is H or CH_3 and X is NH.

10. A process for the preparation of a compound according to any one of claims 1 to 5 comprising

(a) treating a compound of Formula XVII

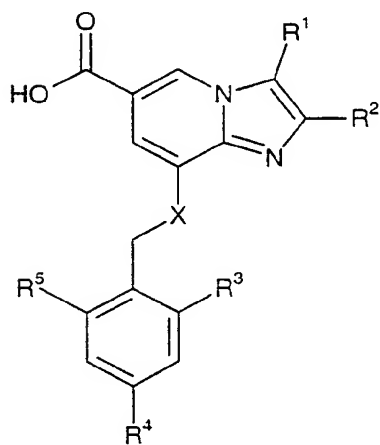
53



XVII

wherein R^1 , R^2 , R^3 , R^4 , R^5 and X are as defined in claim 1 and R^{10} is an alkyl group.
with acid or base under standard conditions to a compound of Formula XVIII

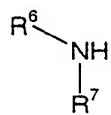
5



XVIII

(b) reacting a compound of Formula XVIII wherein R^1 , R^2 , R^3 , R^4 , R^5 and X is defined in claim 1 with a compound of Formula III

10



III

wherein R⁶ and R⁷ are as defined in claim 1, in the presence of a coupling reagent in an inert solvent under standard conditions, to a compound of Formula I.

11. A compound according to any one of claims 1 to 5 for use in therapy.
12. A pharmaceutical formulation containing a compound according to any one of claims 1 to 5 as active ingredient in combination with a pharmaceutically acceptable diluent or carrier.
13. Use of a compound according to any one of claims 1 to 5 for the manufacture of a medicament for the inhibition of gastric acid secretion.
14. Use of a compound according to any one of claims 1 to 5 for the manufacture of a medicament for the treatment of gastrointestinal inflammatory diseases.
15. Use of a compound according to any one of claims 1 to 5 the manufacture of a medicament for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, wherein the said salt is adapted to be administered in combination with at least one antimicrobial agent.
16. A method for inhibiting gastric acid secretion which comprises administering to a mammal, including man, in need of such inhibition an effective amount of a compound according to any one of claims 1 to 5.
17. A method for the treatment of gastrointestinal inflammatory diseases which comprises administering to a mammal, including man, in need of such treatment an effective amount of a compound according to any one of claims 1 to 5.
18. A method for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, which comprises administering to a mammal, including humans, in need of such treatment an effective amount of a

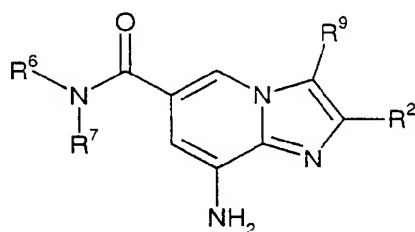
compound as claimed in any one of claims 1 to 5, wherein the said salt is administered in combination with at least one antimicrobial agent.

19. A pharmaceutical formulation for use in the inhibition of gastric acid secretion wherein the active ingredient is a compound according to any one of claims 1 to 5.

20. A pharmaceutical formulation for use in the treatment of gastrointestinal inflammatory diseases wherein the active ingredient is a compound according to any one of claims 1 to 5.

21. A pharmaceutical formulation for use in the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, wherein the active ingredient is a compound according to any one of claims 1 to 5 in combination for simultaneous, separate or sequential use or together with at least one antimicrobial agent.

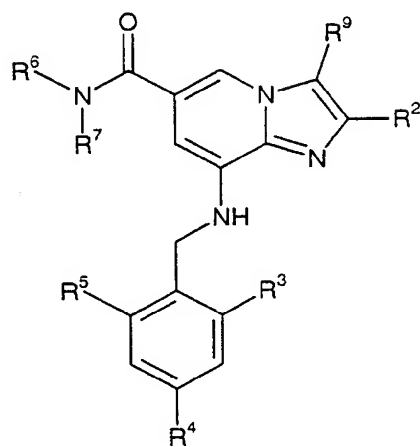
22. A compound of the formula VIII



VIII

wherein R², R⁶ and R⁷ are as defined in claim 1, and R⁹ is H, CH₃ or an ester group.

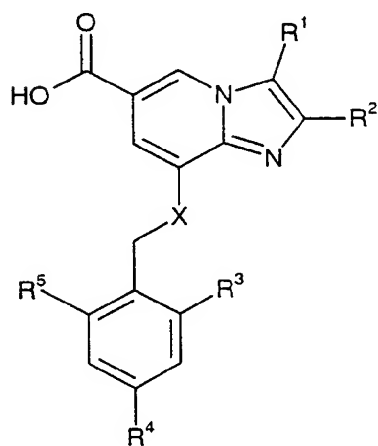
23. A compound of the formula X



X

5 wherein R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined in claim 1, and R^9 is an ester group.

24. A compound of the formula



XVIII

10

wherein R^1 , R^2 , R^3 , R^4 , R^5 and X are as defined in claim 1.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

Astra Aktiebolag
Intellectual Property, Patents
151 85 Södertälje

NOTIFICATION OF DECISION CONCERNING
REQUEST FOR RECTIFICATION

(PCT Rule 91.1(f))

Applicant's or agent's file reference H 2123-1 WO	Date of mailing (day/month/year) 1 8 -06- 1999
International application No. PCT/SE99/00662	REPLY DUE NONE However, see last paragraph below International filing date (day/month/year) 23-04-1999
Applicant Astra Aktiebolag et al	

The applicant is hereby notified that this International Searching Authority has considered the request for rectification of obvious errors in the international application/in other papers submitted by the applicant to this Authority, and that it has decided:


1. ☐ to authorize the rectification:
- ☐ as requested by the applicant.
- ☐ to the extent set forth below*:

2. ☒ to refuse to authorize the rectification or part of it for the following reasons*:

The rectification itself is not obvious in the sense that *anyone* would immediately realize that nothing else could have been intended.

A copy of this notification, together with a copy of the applicant's request for rectification, has been sent to the receiving Office and to the International Bureau.

* If the authorization of the rectification has been refused in whole or in part, the applicant may request the International Bureau, before the technical preparations for international publication have been completed and subject to the payment of a fee, to publish the request for rectification together with the international application. See Rule 91.1(f), third and fourth sentences, and, for the amount of the fee, see the *PCT Applicant's Guide*, Volume I/A, Annex B2(IB).

Name and mailing address of the ISA/ Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. 08-667 72 88	Authorized officer  Telephone No. 08-782 25 00 Jenny Anderberg
---	---



Första Posten

Patent- och Registreringsverket
Box 5055
102 42 STOCKHOLM

June 8, 1999

Our ref.
H 2123-1 WO

Your ref.
PCT/SE99/00662

Re: Request to correct obvious errors according to PCT-rule 91.

Dear Sirs,

We hereby kindly request rectification of the specification of the above identified international patent application in accordance with PCT-rule 91.1(d). The request refers to correction of obvious typing errors.

Please find enclosed substitute sheets, page 11, 14, 19-20, 49, 51-53, and 56, wherein the substituents denoted R^4 and R^5 have been replaced, whereby each and every formula have regained its original substitution pattern found e.g. in the general Formula I on page 2 and in all other related formulas.

We earnestly request that the substitute sheets are included in the present application before publishing.

Yours sincerely,

Christer Hällgren, Ph.D.
Astra AB

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00662

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 471/04, A61K 31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0308917 A2 (FUJISAWA PHARMACEUTICAL, CO., LTD.), 29 March 1989 (29.03.89) --	1-15,19-23
A	J. Med. Chem., Volume 28, 1985, James J. Kaminski et al, "Antiulcer Agents. 1. Gastric Antisecretory and Cytoprotective Properties of Substituted Imidazo(1,2-a)pyridines" page 876 - page 892 --	1-15,19-23
A	EP 0033094 A1 (SCHERING CORPORATION), 5 August 1981 (05.08.81) --	1-15,19-23
A	EP 0228006 A1 (FUJISAWA PHARMACEUTICAL CO., LTD.), 8 July 1987 (08.07.87) --	1-15,19-23

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

9 Sept 1999

Date of mailing of the international search report

09 -09- 1999

Name and mailing address of the ISA/
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Authorized officer

Göran Karlsson/Els
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00662

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0204285 A1 (FUJISAWA PHARMACEUTICAL CO., LTD.), 10 December 1986 (10.12.86) -- -----	1-15,19-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00662

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **16-18**
because they relate to subject matter not required to be searched by this Authority, namely:
**A method for treatment of the human or animal body by therapy,
see rule 39.1**
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-15, 19-23**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00662

The subjects, defined by the problems and their means of solution, as listed below are so different from each other that no technical relationship or interaction can be appreciated to be present so as to form a single general inventive concept. The acceptance of a single general inventive concept covering the end products as well as products used to prepare these and products (intermediates) implies that when several claimed intermediates are implied in different reactions, these intermediates are technically closely inter-connected with the end products as well as with themselves by their use for incorporation of the same essential structural part into the end products.

1. claims 1-15, 19-21, and claims 22 and 23, intermediates VIII and X
2. claim 24, intermediate XVIII

The special technical feature of invention 1 is compound I containing an amide group in position 6 and intermediates VIII and X, which are specially designed for the preparation of compound I. Compounds I, VIII and X do not contain a common technical feature together with intermediate XVIII. Therefore, a single inventive concept based on the relationship intermediates/end products is lacking.

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/08/99

International application No.

PCT/SE 99/00662

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
EP	0308917	A2	29/03/89	AU	2278388	A	06/04/89
				CN	1033628	A	05/07/89
				DK	532088	A	25/03/89
				FI	884318	A	25/03/89
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				AU	540840	B	06/12/84
				AU	6633781	A	30/07/81
				CA	1167845	A	22/05/84
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				FI	810147	A	24/07/81
				GR	72960	A	19/01/84
				HK	94187	A	18/12/87
				IE	50682	B	11/06/86
				JP	56113782	A	07/09/81
				MY	76087	A	31/12/87
				NZ	196071	A	31/05/84
				OA	6727	A	30/06/82
				PT	72370	A,B	01/02/81
				ZA	8100219	A	27/01/82

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				AU	593802	B	22/02/90
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				JP	62187471	A	15/08/87
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				US	4782055	A	01/11/88

EP	0204285	A1	10/12/86	AT	71625	T	15/02/92
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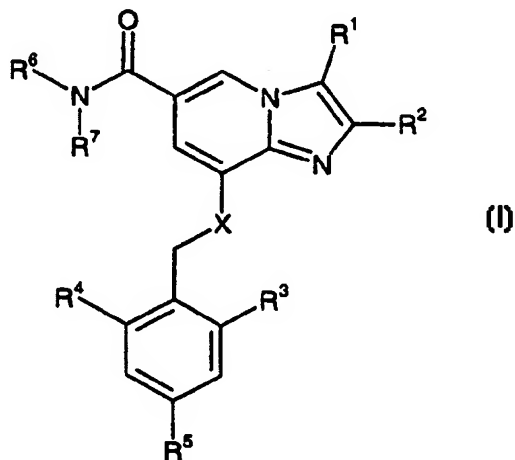
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 471/04, A61K 31/435	A1	(11) International Publication Number: WO 99/55706 (43) International Publication Date: 4 November 1999 (04.11.99)
(21) International Application Number: PCT/SE99/00663 (22) International Filing Date: 23 April 1999 (23.04.99) (30) Priority Data: 9801526-6 29 April 1998 (29.04.98) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): AMIN, Kosrat [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). DAHLSTRÖM, Michael [FI/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). NORDBERG, Peter [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). STARKE, Ingemar [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i> <i>Under Rule 91.1(f), with a request for rectification.</i>

(54) Title: IMIDAZO PYRIDINE DERIVATIVES WHICH INHIBIT GASTRIC ACID SECRETION

(57) Abstract

The present invention relates to imidazo pyridine derivatives of formula (I), in which the phenyl moiety is substituted, and in which the imidazo pyridine moiety is substituted with a carboxamide group in 6-position, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases.



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IMIDAZO PYRIDINE DERIVATIVES WHICH INHIBIT GASTRIC ACID SECRETION

TECHNICAL FIELD

5 The present invention relates to novel compounds, and therapeutically acceptable salts thereof, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions
10 containing at least one compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above. The invention also relates to new intermediates for in the preparation of the novel compounds.

15 BACKGROUND ART

Substituted imidazo[1,2-a]pyridines, useful in the treatment of peptic ulcer diseases, are known in the art, e.g. from EP-B-0033094 and US 4,450,164 (Schering Corporation); from EP-B-0204285 and US 4,725,601 (Fujisawa Pharmaceutical Co.); and from publications by
20 J. J. Kaminski et al. in the Journal of Medical Chemistry (vol. 28, 876-892, 1985; vol. 30, 2031-2046, 1987; vol. 30, 2047-2051, 1987; vol. 32, 1686-1700, 1989; and vol. 34, 533-541, 1991).

For a review of the pharmacology of the gastric acid pump (the H⁺, K⁺-ATPase), see Sachs
25 et al. (1995) Annu. Rev. Pharmacol. Toxicol. 35: 277-305.

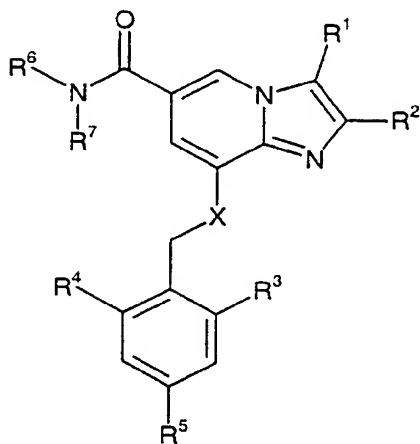
DISCLOSURE OF THE INVENTION

It has surprisingly been found that compounds of the Formula I, which are imidazo
30 pyridine derivatives in which the phenyl moiety is substituted, and in which the imidazo pyridine moiety is substituted with a carboxamide group in 6-position are particularly

effective as inhibitors of the gastrointestinal H^+ , K^+ -ATPase and thereby as inhibitors of gastric acid secretion.

In one aspect, the invention thus relates to compounds of the general Formula I

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I

or a pharmaceutically acceptable salt thereof, wherein

10 R^1 is

- (a) H,
- (b) CH_3 , or
- (c) CH_2OH ;

15 R^2 is

- (a) CH_3
- (b) CH_2CH_3

R^3 is

- 20 (a) H
- (b) C_1 - C_6 alkyl,
- (c) hydroxylated C_1 - C_6 alkyl
- (d) halogen

25 R^4 is

- (a) H,
- (b) C₁-C₆ alkyl,
- (c) hydroxylated C₁-C₆ alkyl, or
- (d) halogen;

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R⁵ is

- (a) H, or
- (b) halogen;

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R⁶, R⁷ are the same or different

- (a) H,
- (b) C₁-C₆ alkyl;
- (c) hydroxylated C₁-C₆ alkyl
- (d) C₁-C₆ alkoxy-substituted C₁-C₆ alkyl

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X is

- (a) NH, or
- (b) O.

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As used herein, the term "C₁-C₆ alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said C₁-C₆ alkyl include methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

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The term "halogen" includes fluoro, chloro, bromo and iodo.

Both the pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers are within the scope of the invention. It should be understood that all the diastereomeric forms possible (pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers) are within the scope of the invention. Also included in the invention are derivatives of the compounds of the Formula I which have the biological function of the compounds of the Formula I, such as prodrugs.

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It will also be appreciated by those skilled in the art, although derivatives of compounds of formula I may not possess pharmacological activity as such, they may be administered parenterally or orally and thereafter metabolised in the body to form compounds of the invention which are pharmacologically active. Such derivatives may therefore be described as "prodrugs". All prodrugs of compounds of formula I are included within the scope of the invention.

Depending on the process conditions the end products of the Formula I are obtained either in neutral or salt form. Both the free base and the salts of these end products are within the scope of the invention.

Acid addition salts of the new compounds may in a manner known *per se* be transformed into the free base using basic agents such as alkali or by ion exchange. The free base obtained may also form salts with organic or inorganic acids.

In the preparation of acid addition salts, preferably such acids are used which form suitably therapeutically acceptable salts. Examples of such acids are hydrohalogen acids such as hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxyl or sulphonic acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, p-hydroxybenzoic acid, embonic acid, methanesulphonic acid, ethanesulphonic acid, hydroxyethanesulphonic acid, halogenbensenesulphonic acid, toluenesulphonic acid or naphthalenesulphonic acid.

Preferred compounds according to the invention are those of the Formula I wherein R^1 is CH_3 or CH_2OH ; R^2 is CH_3 or CH_2CH_3 ; R^3 is CH_3 or CH_2CH_3 ; R^4 is CH_3 or CH_2CH_3 ; R^5 is H, Br, Cl, or F.

Particularly preferred compounds according to the invention are:

- 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-propyl-imidazo[1,2-a]pyridine-6-carboxamide
- 8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-6-carboxamide
- 5 • 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide
- 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide
- 8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide
- 8-(2-ethyl-6-methylbenzylamino)-N,N,2,3-tetramethylimidazo[1,2-a]pyridine-6-carboxamide
- 10 • 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide
- 2,3-dimethyl-8-(2-ethyl-4-fluoro-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate
- 2,3-dimethyl-8-(2-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide
- 15 • 2,3-dimethyl-8-(2,6-dimethyl-4-fluoro-benzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate
- 2,3-dimethyl-8-(2-methyl-6-isopropylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate
- 2,3-dimethyl-8-(2,6-diethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide
- 20 • 2,3-dimethyl-8-(2-ethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide
- 2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide
- N-(2,3-dihydroxypropyl)-2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-[1,2-a]pyridine-6-carboxamide
- 25 • 2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-(2-methoxyethyl)-imidazo[1,2-a]pyridine-6-carboxamide
- 2-methyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide
- 2,3-dimethyl-8-(2-bromo-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide
- 2,3-dimethyl-8-(2-(2-hydroxyethyl)-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide
- 30 • 8-(2-ethyl-6-methylbenzylamino)-N,N-bis(2-hydroxyethyl)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide
- 8-(2-ethyl-6-methylbenzylamino)-N-(2-hydroxyethyl)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide

- 2,3-dimethyl-8-(2-ethyl-6-methylbenzyloxy)-imidazo[1,2-a]pyridine-6-carboxamide

Most preferred compounds according to the invention are:

- 8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-6-carboxamide
- 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide
- 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide
- 8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide
- 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide
- 2,3-dimethyl-8-(2-ethyl-4-fluoro-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide
- 2,3-dimethyl-8-(2,6-dimethyl-4-fluoro-benzylamino)-imidazo[1,2-a]pyridine-6-carboxamide
- 2,3-dimethyl-8-(2,6-diethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide
- 2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide
- 2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-(2-methoxyethyl)-imidazo[1,2-a]pyridine-6-carboxamide

Preparation

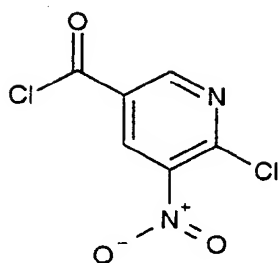
The present invention also provides the following processes A, B and C for the manufacture of compounds with the general Formula I.

Process A

Process A for manufacture of compounds with the general Formula I wherein X is NH comprises the following steps:

- a) Compounds of the general Formula II

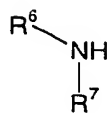
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II

can be reacted with amino compounds of the general Formula III

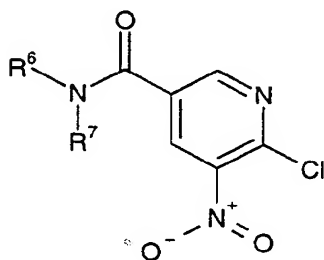
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III

wherein R⁶ and R⁷ are as defined for Formula I, to the corresponding amide of the Formula IV. The reaction can be carried out in standard conditions in an inert solvent.

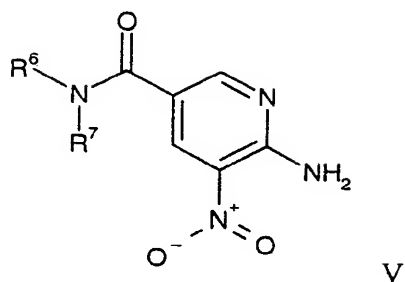
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IV

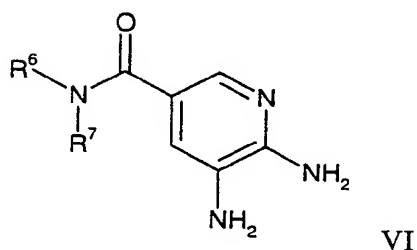
b) Compounds of the general Formula IV can be reacted with ammonia to compounds of the general Formula V

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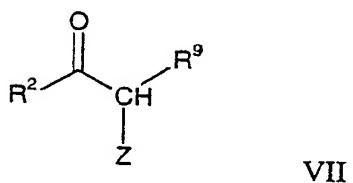
wherein R^6 and R^7 are as defined for Formula I. The reactions can be carried out under standard conditions in an inert solvent.

c) Compounds of the Formula V can be reduced e.g. by using hydrogen and a catalyst such as Pd/C to compounds of the Formula VI



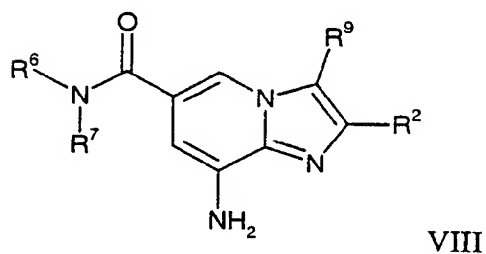
wherein R^6 and R^7 are as defined for Formula I. The reaction can be carried out under standard conditions in an inert solvent.

d) The imidazo[1,2-a]pyridine compounds of the Formula VIII can be prepared by reacting compounds of the general Formula VI with compounds of the general Formula VII



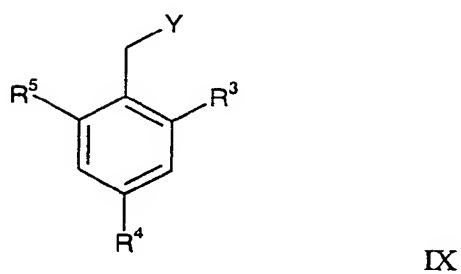
wherein R^2 is as defined for Formula I and Z is a leaving group such as halogen, mesyl, tosyl and R^9 represents H, CH_3 or an ester group such as $COOCH_3$, $COOC_2H_5$ etc.

The reaction is carried out under standard conditions in an inert solvent such as acetone, acetonitrile, alcohol, dimethylformamide, etc. with or without a base.

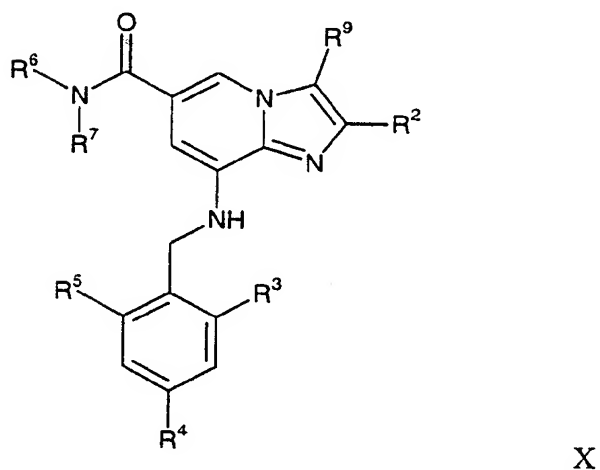


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e) Compounds of the Formula VIII can be reacted with compounds of the Formula IX



10 wherein R³, R⁴ and R⁵ are as defined for Formula I and Y is a leaving group, such as a halide, tosyl or mesyl, to the compounds of the Formula X.



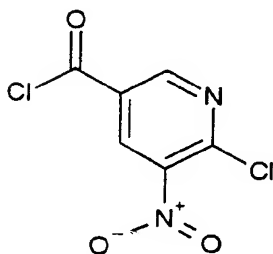
wherein R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for Formula I and R^9 is H, CH_3 or an ester group such as $COOCH_3$, $COOC_2H_5$, etc. It is convenient to conduct this reaction in an inert solvent, e.g. acetone, acetonitrile, dimethoxyethane, methanol, ethanol or dimethylformamide with or without a base. The base is e.g. an alkali metal hydroxide, such as sodium hydroxide and potassium hydroxide, an alkali metal carbonate, such as potassium carbonate and sodium carbonate; or an organic amine, such as triethylamine.

f) Reduction of compounds of the general Formula X wherein R^9 is an ester group e.g. by using lithium borohydride in an inert solvent such as tetrahydrofuran or diethyl ether, to the compounds of the general Formula I wherein R^1 is CH_2OH .

Process B

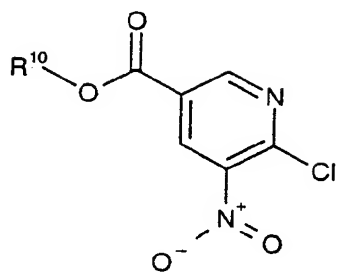
Process B for manufacture of compounds with the general Formula I wherein R^1 is H or CH_3 and X is NH comprises the following steps:

a) Compounds of the general Formula II



II

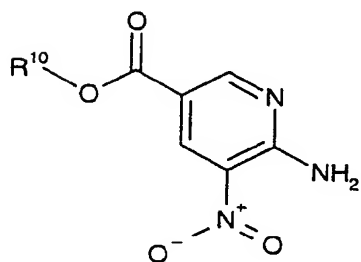
can be reacted with an alcohol compound of the general Formula $R^{10}-OH$, wherein R^{10} is an alkyl group such as methyl, ethyl, etc. to the corresponding ester of Formula XI.



XI

The reactions can be carried out under standard conditions .

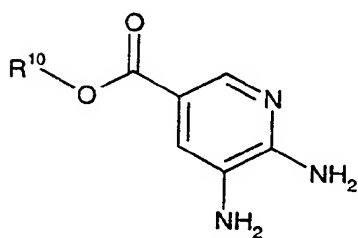
- 5 b) Compounds of the general Formula XI can be reacted with ammonia to compounds of the general Formula XII



XII

- 10 wherein R^{10} is an alkyl group such as methyl or ethyl, etc. The reactions can be carried out under standard conditions in an inert solvent.

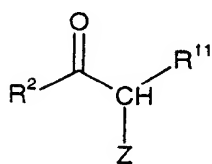
- c) Compounds of the Formula XII can be reduced e.g. by using hydrogen and a catalyst such as Pd/C to compounds of the Formula XIII



XIII

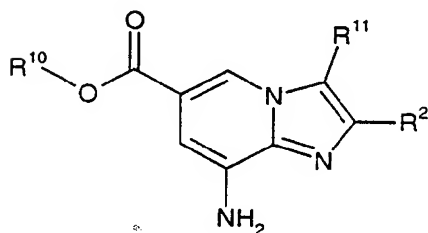
wherein R^{10} is an alkyl group such as methyl, ethyl etc. The reaction can be carried out under standard conditions in an inert solvent.

- 5 d) The imidazo[1,2-a]pyridine compounds of the Formula XV wherein R^{10} is an alkyl group such as methyl, ethyl etc, can be prepared by reacting compounds of the general Formula XIII with compounds of the general Formula XIV



XIV

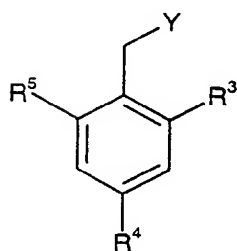
- 10 wherein R^2 is as defined for Formula I, Z is a leaving group such as halogen, mesyl or tosyl and R^{11} represents H or CH_3 . The reaction is carried out under standard conditions in an inert solvent such as acetone, acetonitrile, alcohol, dimethylformamide etc, with or without a base.



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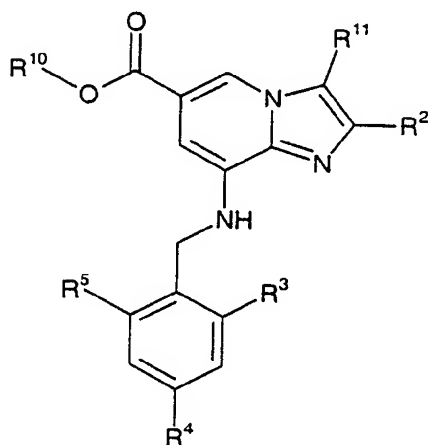
XV

- e) Compounds of the Formula XV can be reacted with compounds of the Formula IX



IX

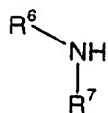
wherein R^3 , R^4 and R^5 are as defined for Formula I and Y is a leaving group, such as a halide, tosyl or mesyl, to the compounds of the Formula XVI.



XVI

wherein R^2 , R^3 , R^4 and R^5 are as defined for Formula I, R^{10} is an alkyl group such as methyl, ethyl, etc. and R^{11} is H, or CH_3 . It is convenient to conduct this reaction in an inert solvent, e.g. acetone, acetonitrile, dimethoxyethane, methanol, ethanol or dimethylformamide with or without a base. The base is e.g. an alkali metal hydroxide, such as sodium hydroxide and potassium hydroxide, an alkali metal carbonate, such as potassium carbonate and sodium carbonate; or an organic amine, such as triethylamine.

f) Compounds of the Formula XVI can be reacted with amino compounds of the general Formula III



III

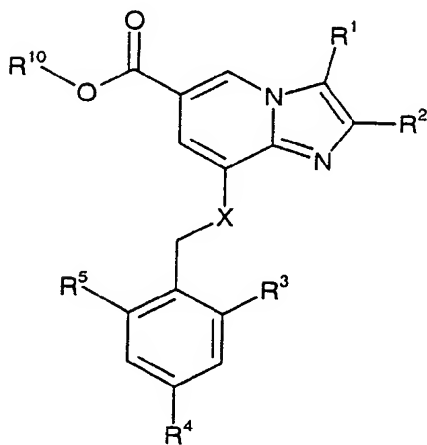
wherein R^6 and R^7 are as defined in Formula I to the corresponding amide of the Formula I wherein R^1 is H or CH_3 and X is NH. The reaction can be carried out by heating the reactants in the neat amino compound or in an inert solvent under standard conditions.

Process C

Process C for manufacture of compounds with the general Formula I comprises the following steps:

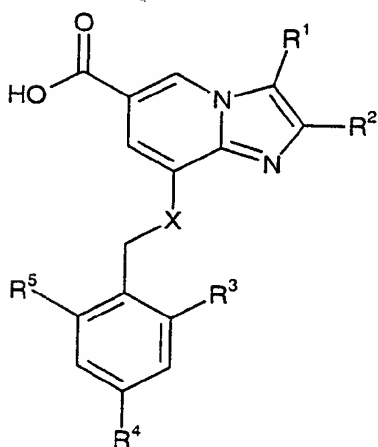
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a) Treating compounds of Formula XVII



XVII

10 wherein R¹, R², R³, R⁴, R⁵, and X are as defined in Formula I and R¹⁰ is an alkyl group such as methyl, ethyl, etc, with acid or base under standard conditions can hydrolyzed them to the corresponding carboxylic acid compounds of Formula XVIII



XVIII

b) Compounds of the Formula XVIII wherein R¹, R², R³, R⁴, R⁵ and X are as defined in Formula I can be reacted with amino compounds of Formula III in the presence of a coupling reagent to the corresponding amide compounds of the Formula I. The reaction can be carried out in an inert solvent under standard conditions.

5

Medical use

In a further aspect, the invention relates to compounds of the formula I for use in therapy, in particular for use against gastrointestinal inflammatory diseases. The invention also provides the use of a compound of the formula I in the manufacture of a medicament for the inhibition of gastric acid secretion, or for the treatment of gastrointestinal inflammatory diseases.

The compounds according to the invention may thus be used for prevention and treatment of gastrointestinal inflammatory diseases, and gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable, e.g. in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre-and postoperatively to prevent acid aspiration and stress ulceration.

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 1000 mg per day of active substance.

Pharmaceutical formulations

In yet a further aspect, the invention relates to pharmaceutical compositions containing at least one compound of the invention, or a therapeutically acceptable salt thereof, as active
5 ingredient.

The compounds of the invention can also be used in formulations together with other active ingredients, e.g. antibiotics such as amoxicillin.

10 For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. The pharmaceutical formulation contains at least one compound of the invention in combination with one or more pharmaceutically acceptable ingredients. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical
15 preparations are a further object of the invention. Usually the amount of active compounds is between 0.1–95% by weight of the preparation, preferably between 0.1–20% by weight in preparations for parenteral use and preferably between 0.1 and 50% by weight in preparations for oral administration.

20 In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium
25 stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets.

Soft gelatin capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for
30 soft gelatin capsules. Hard gelatin capsules may contain granules of the active compound. Hard gelatin capsules may also contain the active compound in combination with solid

powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Dosage units for rectal administration may be prepared (i) in the form of suppositories which contain the active substance mixed with a neutral fat base; (ii) in the form of a gelatin rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatin rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.1% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain coloring agents, flavoring agents, saccharine and carboxymethyl cellulose or other thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from 0.1% to 10% by weight. These solutions may also contain stabilizing ingredients and/or buffering ingredients and are dispensed into unit doses in the form of ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extemporaneously before use.

The compounds according to the present invention can also be used in formulations, together or in combination for simultaneous, separate or sequential use, with other active ingredients, e.g. for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa. Such other active ingredients may be antimicrobial agents, in particular:

- β -lactam antibiotics such as amoxicillin, ampicillin, cephalothin, cefaclor or cefixime;
- macrolides such as erythromycin, or clarithromycin;
- tetracyclines such as tetracycline or doxycycline;
- aminoglycosides such as gentamycin, kanamycin or amikacin;
- 5 • quinolones such as norfloxacin, ciprofloxacin or enoxacin;
- others such as metronidazole, nitrofurantoin or chloramphenicol; or
- preparations containing bismuth salts such as bismuth subcitrate, bismuth subsalicylate, bismuth subcarbonate, bismuth subnitrate or bismuth subgallate.

10 The compounds according to the present invention can also be used together or in combination for simultaneous, separate or sequential use with antacids such as aluminium hydroxide, magnesium carbonate and magnesium hydroxid or alginic acid, or together or in combination for simultaneous, separate or sequential use with pharmaceuticals which inhibit acid secretion, such as, H₂-blockers (*e.g.* cimetidine, 15 ranitidine), H⁺/K⁺ - ATPase inhibitors (*e.g.* omeprazole, pantoprazole, lansoprazole or rabeprazole), or together or in combination for simultaneous, separate or sequential use with gastroprokinetics (*e.g.* cisapride or mosapride).

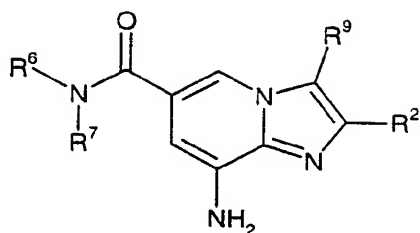
20 *Intermediates*

A further aspect of the invention is new intermediate compounds which are useful in the synthesis of compounds according to the invention.

25 Thus, the invention includes

(a) a compound of the formula VIII

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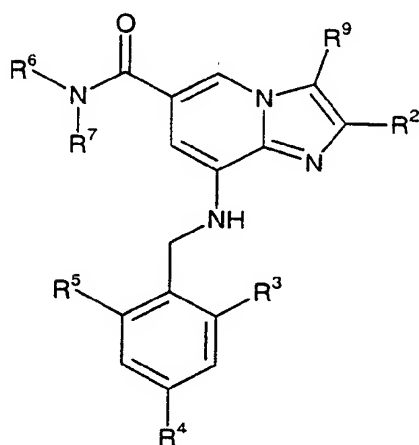


VIII

wherein R^2 , R^6 and R^7 are as defined for Formula I, and R^9 is H, CH_3 or an ester group such as $COOCH_3$, $COOC_2H_5$, etc.;

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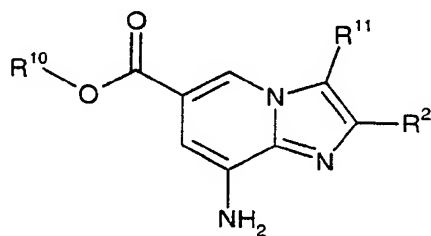
(b) a compound of the formula X



X

10 wherein R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for Formula I, and R^9 is an ester group such as $COOCH_3$, $COOC_2H_5$ etc.;

(c) a compound of the formula XV

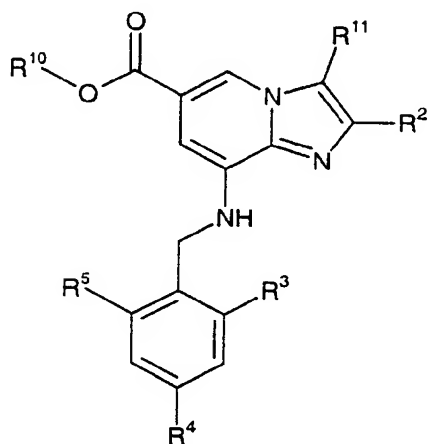


XV

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wherein R^2 is as defined for Formula I, R^{10} is an alkyl group and R^{11} is H or CH_3 ;

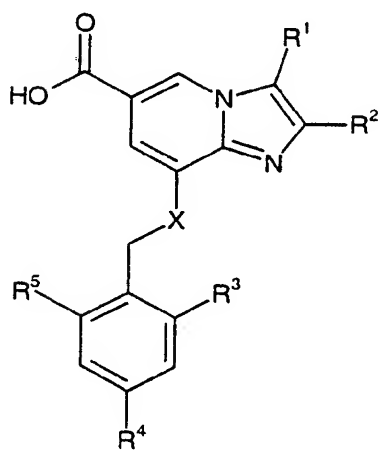
(d) a compound of the formula XVI



XVI

wherein R^2 , R^3 , R^4 and R^5 are as defined for Formula I, R^{10} is an alkyl group and R^{11} is H or CH_3 ;

(e) a compound of the formula XVIII



XVIII

wherein R^1 , R^2 , R^3 , R^4 , R^5 and X are as defined for

Formula I.

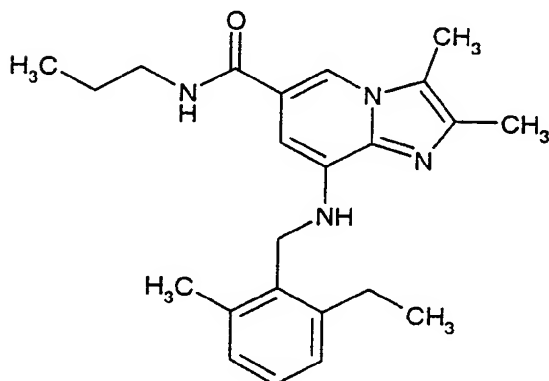
EXAMPLES

5

1. PREPARATION OF COMPOUNDS OF THE INVENTION

Example 1.1

- 10 *Synthesis of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-propyl-imidazo[1,2-a]pyridine-6-carboxamide*

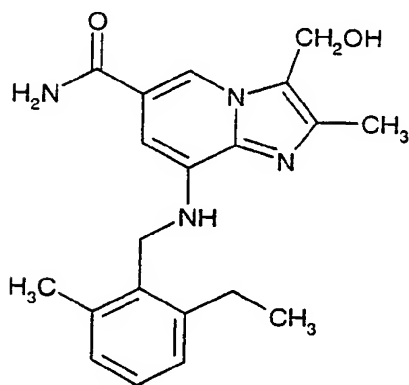


- 15 Ethyl 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylate (0.12 g, 0.33 mmol), propylamine (1.0 g, 17 mmol) and a cat. amount of sodium cyanide were refluxed in methanol (20 ml) for 24 h. An additional amount of propylamine (1.0 g, 17 mmol) was added and the reaction mixture was refluxed for 24 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using diethyl ether as eluent. Crystallization from diethyl ether gave 0.053 g (42%) of the title compound.
- 20

¹H-NMR (300 MHz, CDCl₃): δ 1.0 (t, 3H), 1.2 (t, 3H), 1.65-1.75 (m, 2H), 2.3 (s, 3H), 2.35 (s, 3H), 2.38 (s, 3H), 2.7 (q, 2H), 3.4-3.5 (m, 2H), 4.35 (d, 2H), 4.9 (bs, 1H), 6.2 (bs, 1H), 6.35 (s, 1H), 7.0-7.2 (m, 4H), 7.85 (s, 1H).

5 *Example 1.2*

Synthesis of 8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-6-carboxamide



10

Ethyl 6-(aminocarbonyl)-8-(2-ethyl-6-methylbenzylamino)-2-methylimidazo[1,2-a]pyridine-3-carboxylate (280 mg, 0.71 mmol) and lithium borohydride (16 mg, 0.71 mmol) were added to tetrahydrofuran (10 ml) and the reaction mixture was refluxed for 70 min. Additional amounts of lithium borohydride (16 mg) and methanol (45 mg, 1.42 mmol) were added and the mixture was refluxed for 80 min. Additional amounts of lithium borohydride (16 mg) and methanol (22 mg, 71 mmol) were added and the mixture was refluxed for 4 h. The reaction mixture was allowed to reach R.T. and water (1 ml) and methanol (5 ml) and was stirred for 40 min. at R.T. The solvents were evaporated under reduced pressure and the residue was added to water and was stirred for 80 min. The crystals were filtered off and washed with water, ethyl acetate/ethanol and diethyl ether to give the desired product (115 mg, 46 %).

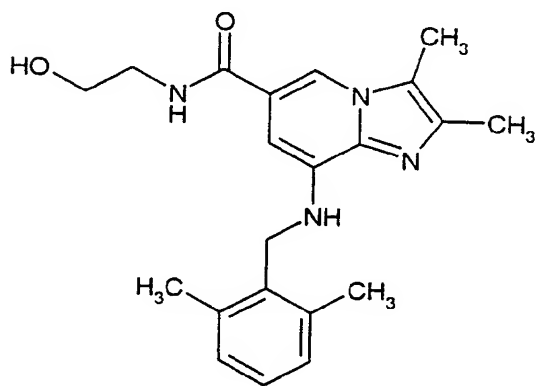
15

20

¹H-NMR (300 MHz, DMSO-d₆): δ 1.15 (t, 3H), 2.25 (s, 3H), 2.35 (s, 3H), 2.7 (q, 2H), 4.35 (d, 2H), 4.75 (d, 2H), 4.85 (t, 1H), 5.1 (t, 1H), 6.8 (s, 1H), 7.1-7.25 (m, 3H), 7.4 (bs, 1H), 8.05 (bs, 1H), 8.3 (s, 1H)

5 *Example 1.3*

Synthesis of 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide



10

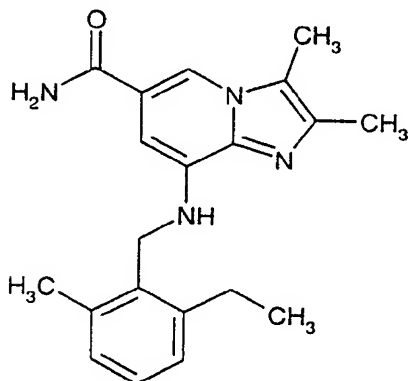
Methyl 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylate (0.12 g, 0.33 mmol), ethanolamine (0.2 g, 3.3 mmol) and sodium cyanide (10 mg, 0.2 mmol) were refluxed in dimethoxyethane (2 ml) for 20 h. The solvent was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using methylene chloride : methanol (92:8) as eluent gave the product which was washed with diethyl ether to give 103 mg (79%) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 2.3 (s, 6H), 2.35 (s, 6H), 3.5-3.6 (m, 2H), 3.75-3.8 (m, 2H), 4.3 (d, 2H), 4.95 (t, 1H), 6.4 (s, 1H), 6.85 (t 1H), 7.0-7.2 (m, 3H), 7.75 (s, 1H)

20

*Example 1.4**Synthesis of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide*

5

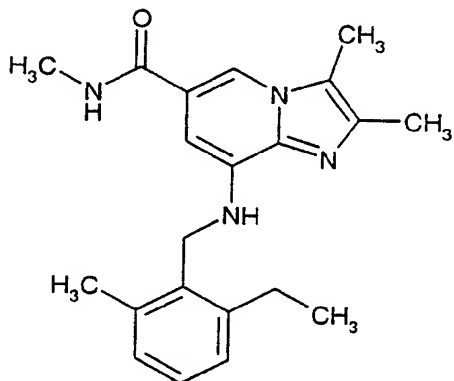


8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide (3.3 g, 16.2 mmol), 2-ethyl-6-methylbenzylchloride (2.73 g, 16.2 mmol), potassium carbonate (8.0 g, 58 mmol) and
10 potassium iodide (1.1 g, 6.6 mmol) were added to acetone (150 ml) and refluxed for 20 h. An additional amount of 2-ethyl-6-methylbenzylchloride (1.0 g, 5.9 mmol) was added and the reaction mixture was refluxed for 7 h. Methylene chloride (60 ml) and methanol (30 ml) were added. The reaction mixture was filtered and the solvents were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using
15 methylene chloride: methanol (100:7) as eluent. Crystallization from ethyl acetate gave 2.8 g (50%) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 1.2 (t, 3H), 2.34 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.7 (q, 2H), 4.4 (d, 2H), 4.9 (bs, 1H), 6.0 (bs, 2H), 6.45 (s, 1H), 7.0-7.2 (m, 3H), 7.9, (s, 1H).

*Example 1.5**Synthesis of 8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide*

5



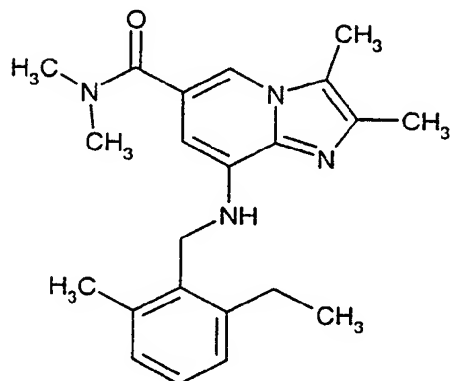
2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium
 10 tétrafluoroborate (TBTU) (0.14 g, 0.44 mmol) were added to methylene chloride (10 ml) and the reaction mixture was stirred at room temperature for 15 min. Methylamine (0.1 g, 3.2 mmol) was added and the reaction mixture was stirred at ambient temperature for 1.5 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using ethylacetate : methylene chloride (1:1) as eluent. The
 15 yield was treated with diethyl ether to give 40 mg (26 %) of the desired product .

¹H-NMR (300 MHz, CDCl₃): δ 1.2 (t, 3H), 2.33 (s, 3H), 2.36 (s, 3H), 2.38 (s, 3H), 2.7 (q, 2H), 3.05 (d, 3H), 4.35 (d, 2H), 4.9 (t, 1H), 6.3 (bs, 1H), 6.4 (s, 1H), 7.0-7.2 (m, 3H), 7.85 (s, 1H)

20

*Example 1.6**Synthesis of 8-(2-ethyl-6-methylbenzylamino)-N,N,2,3-tetramethylimidazo[1,2-a]pyridine-6-carboxamide*

5

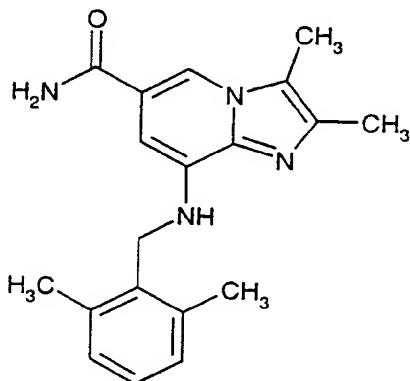


2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium
 10 tetrafluoroborate (TBTU) (0.14 g, 0.44 mmol) were added to methylene chloride (10 ml). Dimethylamin (0.063 g, 1.4 mmol) was added and the reaction mixture was stirred at ambient temperature for 4 h. An additional amount of dimethylamin (0.1 ml) was added and the mixture was stirred at room temperature for 20 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography using
 15 methylene chloride : methanol (9:1) as eluent. The oily product was treated with heptane and the solid that formed was filtered off to give 0.1 g (62 %) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 1.2 (t, 3H), 2.35 (s, 6H), 2.4 (s, 3H), 2.7 (q, 2H), 3.15 (s, 6H), 4.4 (d, 2H), 4.9 (t, 1H), 6.25 (s, 1H), 7.0-7.2 (m, 3H), 7.45 (s, 1H)

*Example 1.7**Synthesis of 2,3-dimethyl-8-(2,6-dimethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide*

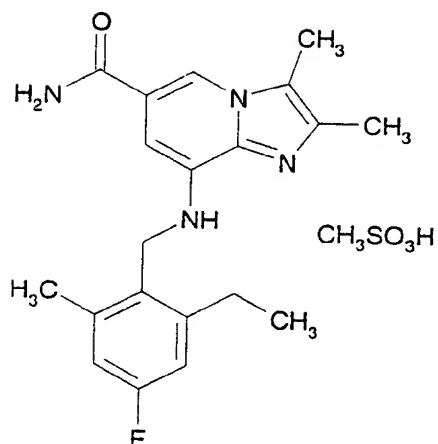
5



8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide (0.6 g, 2.9 mmol), 2,6-dimethylbenzylchloride (0.45 g, 2.9 mmol), sodium carbonate (1.0 g, 9.4 mmol) and potassium iodide (0.2 g, 1.3 mmol) were added to acetone (25 ml) and refluxed for 19 h. Methylene chloride was added and inorganic salts were filtered off. The solution was washed with a bicarbonate solution, the organic layer was separated, dried and the solvents were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using methylene chloride : methanol (100 : 5) as eluent and the product was washed with diethyl ether to give 0.78 g (82 %) of the title compound.

¹H-NMR (500 MHz, CDCl₃): δ 2.33 (s, 3H), 2.4 (s, 6H), 2.42 (s, 3H), 4.4 (d, 2H), 2.95 (bs, 1H), 6.45 (s, 1H), 7.05-7.15 (m, 3H), 7.95 (s, 1H)

*Example 1.8**Synthesis of 2,3-dimethyl-8-(2-ethyl-4-fluoro-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate*

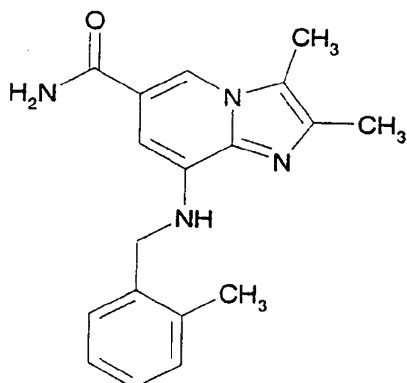


8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (0.7 g, 1.9 mmol),
 2-ethyl-4-fluoro-6-methylbenzylchloride (0.26 g, 1.9 mmol) and diisopropylethylamin
 (0.54 g, 4.2 mmol) were added to dimethylformamide (5 ml) and stirred at room
 temperature for 1 h. Methylene chloride and water were added to the reaction mixture, the
 organic layer was separated, dried and evaporated under reduced pressure. The residue was
 solved in ethylacetate and ethanol and metanesulfonic acid (0.2 g, 2 mmol) was added. The
 product was filtered off and was solved in methylene chloride:methanol (2:1) and an excess
 of potassium carbonate. The solids were filtered off and the solvent was evaporated under
 reduced pressure. The residue was purified by column chromatography on silica gel using
 methylene chloride: methanol (10:1) as eluent. The residue was solved in ethylacetate and
 methansulfonic acid (0.04 g, 0.4 mmol) was added. The salt was filtered off to give 0.2 g
 (23 %) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ 1.15 (t, 3H), 2.25 (s, 3H), 2.35 (s, 3H), 2.4 (s, 3H), 2.45
 (s, 3H), 2.6 (q, 2H), 4.35 (d, 2H), 6.15 (bs, 1H), 6.95-7.05 (m, 2H), 7.4 (s, 1H), 7.8 (bs,
 1H), 8.3 (bs, 1H), 8.45 (s, 1H)

Example 1.9

Synthesis of 2,3-dimethyl-8-(2-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide

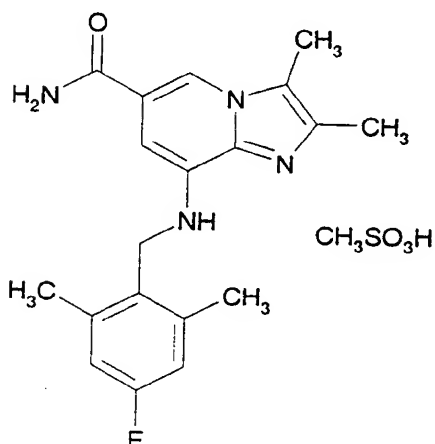


8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (1.0 g, 2.7 mmol), α -chloro-o-xylene (0.38 g, 2.7 mmol) and diisopropylethylamin (0.76 g, 5.9 mmol) in dimethylformamide (7 ml) were stirred at 50 °C for 7 h and at room temperature for 72 h. The solvent was evaporated and the residue was treated with a mixture of methylene chloride, water and a small amount of diisopropylethylamin. The solid that formed was isolated by filtration and washed with ethylacetate to give 0.11 g (13 %) of the title compound.

$^1\text{H-NMR}$ (300 MHz, DMSO- d_6): δ 2.3 (s, 3H), 2.35 (s, 3H), 2.4 (s, 3H), 4.45 (d, 2H), 6.3-6.4 (m, 2H), 7.1-7.25 (m, 4H), 7.3 (bs, 1H), 7.85 (bs, 1H), 8.05 (s, 1H)

Example 1.10

Synthesis of 2,3-dimethyl-8-(2,6-dimethyl-4-fluorobenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate

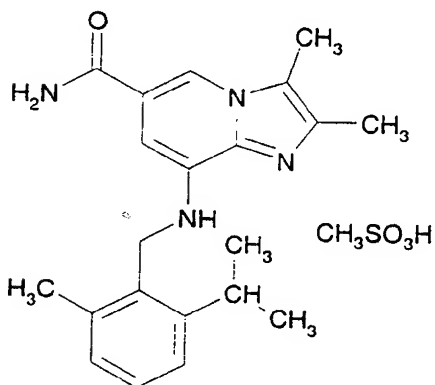


8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (5.0 g, 13.4 mmol), 2,6-dimethyl-4-fluorobenzylbromide (2.91 g, 13.4 mmol), diisopropylethylamin (3.8 g, 29.5 mmol) and a cat. amount of potassium iodide were stirred in dimethylformamide (20 ml) at room temperature overnight. Water (70 ml) and methylene chloride (2 x 50 ml) were added to the reaction mixture and the organic layer was separated, dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using methylene chloride: methanol (9:1) as eluent. The product was solved in isopropanol and methansulfonic acid (0.3 g) was added. The salt that formed was isolated by filtration and washed with isopropanol and diethyl ether to give 1.4 g (24 %) of the title compound.

$^1\text{H-NMR}$ (500 MHz, DMSO- d_6): δ 2.25 (s, 3H), 2.35 (s, 6H), 2.4 (s, 3H), 2.5 (s, 3H), 4.4 (d, 2H), 6.1 (bs, 1H), 7.0 (d, 2H), 7.35 (s, 1H), 7.8 (bs, 1H), 8.3 (bs, 1H), 8.45 (s, 1H)

Example 1.11

Synthesis of 2,3-dimethyl-8-(2-methyl-6-isopropylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate



20

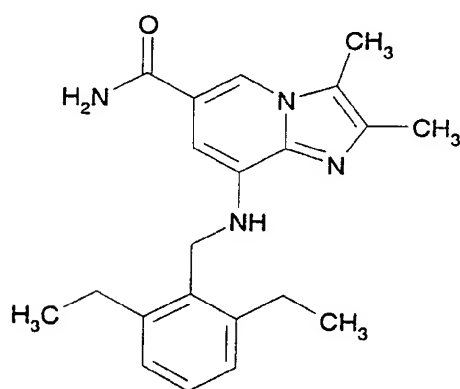
8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (3.0 g, 8.0 mmol), 2-methyl-6-isopropylbenzylchloride (1.47 g, 8.0 mmol), diisopropylethylamin (2.4 g, 18.6 mmol) and a cat. amount of potassium iodide in dimethylformamide (15 ml). The title compound were prepared according to Example 1.10 (Yield: 1.3 g, 36 %)

25

¹H-NMR (300 MHz, DMSO-d₆): δ 1.2 (d, 6H), 2.25 (s, 3H), 2.4 (s, 3H), 2.45 (s, 3H), 2.5 (s, 3H), 3.2 (m, 1H), 4.45 (d, 2H), 6.15 (bs, 1H), 7.15-7.3 (m, 3H), 7.4 (s, 1H), 7.85 (bs, 1H), 8.35 (bs, 1H), 8.45 (s, 1H)

5 *Example 1.12*

Synthesis of 2,3-dimethyl-8-(2,6-diethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide



10

8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (4.0 g, 10.7 mmol), 2,6-diethylbenzylchloride (1.8 g, 9.9 mmol), diisopropylethylamin (3.0 g, 23.3 mmol) were stirred in dimethylformamide (20 ml) at 50 °C overnight and at 70 °C for 3 h. Water (60 ml) and methylene chloride were added and the organic layer was separated, dried and evaporated under reduced pressure. The residue was treated with diethyl ether and the product was filtered off to give 1.7 g (45 %) of the title compound.

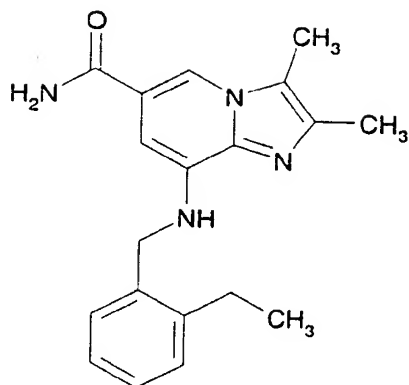
¹H-NMR (300 MHz, CDCl₃): δ 1.2 (t, 6H), 2.35 (s, 3H), 2.4 (s, 3H), 2.7 (q, 4H), 4.4 (d, 2H), 4.95 (bs, 1H), 6.15 (bs, 2H), 6.5 (s, 1H), 7.05-7.25 (m, 3H), 7.95 (s, 1H)

20

Example 1.13

Synthesis of 2,3-dimethyl-8-(2-ethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide

25



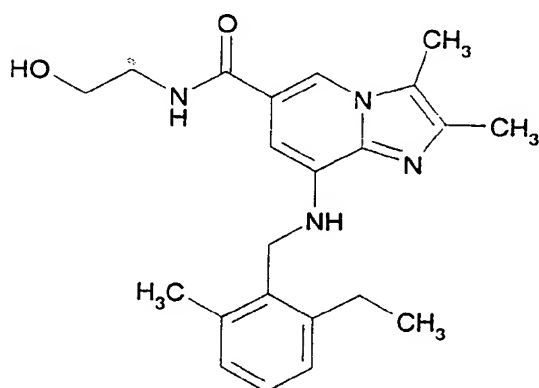
8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (4.0 g, 10.7 mmol),
2-ethylbenzylchloride (1.65 g, 10.7 mmol), diisopropylethylamin (3.0 g, 23.3 mmol) in
diethylformamide (20 ml).

The title compound was prepared according to Example 1.12 (Yield: 1.15 g, 26 %)

¹H-NMR (300 MHz, CDCl₃): δ 1.2 (t, 3H), 2.3 (s, 3H), 2.35 (s, 3H), 2.75 (q, 2H), 4.5 (d, 2H), 6.3 (t, 1H), 6.4 (s, 1H), 7.05-7.25 (m, 4H), 7.3 (bs, 1H), 7.85 (bs, 1H), 8.05 (s, 1H)

Example 1.14

Synthesis of 2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide



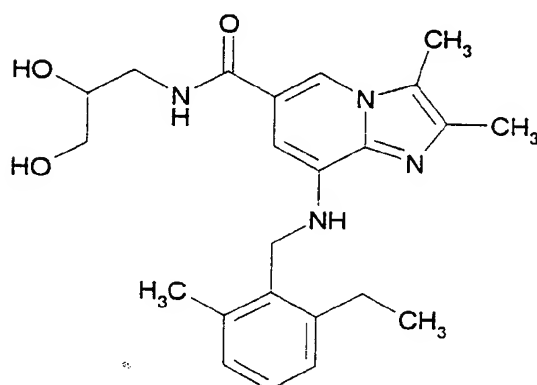
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid
(0.3 g, 0.88 mmol) and o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium
tetrafluoroborate (TBTU)(0.29 g, 0.90 mmol) were added to methylene chloride (15 ml)

and the mixture was stirred for 5 min. Ethanolamin (0.11 g, 1.8 mmol) was added and the reaction mixture was stirred at ambient temperature for 2 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using methylene chloride:methanol (9:1) as eluent. Crystallization from diethyl ether gave 0.2 (59 %) of the desired product.

¹H-NMR (500 MHz, CDCl₃): δ 1.2 (t, 3H), 2.3 (s, 6H), 2.35 (s, 3H), 2.7 (q, 2H), 3.55-3.6 (m, 2H), 3.8-3.85 (m, 2H), 4.35 (d, 2H), 4.9 (t, 1H), 6.4 (s, 1H), 6.85 (t, 1H), 7.05-7.2 (m, 3H), 7.75 (s, 1H)

Example 1.15

Synthesis of N-(2,3-dihydroxypropyl)-2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-[1,2-a]pyridine-6-carboxamide



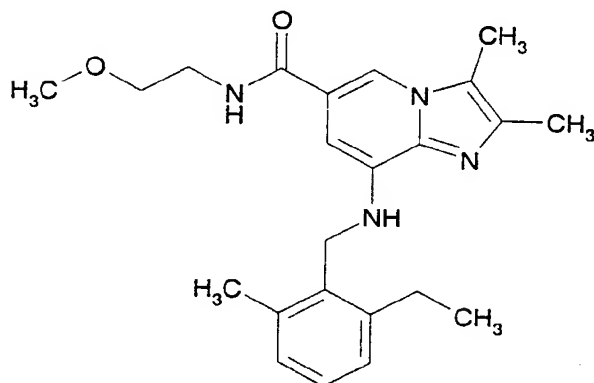
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.3 g, 0.88 mmol), o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU) (0.29 g, 0.90 mmol) and 3-amino-1,2-propanediol (0.16 g, 1.81 mmol) in dimethylformamide (10 ml).

The title compound was prepared according to Example 1.14 (Yield: 0.2 g, 54 %)

¹H-NMR (500 MHz, CDCl₃): δ 1.2 (t, 3H), 1.82-1.85 (m, 1H), 2.32 (s, 3H), 2.33 (s, 3H), 2.36 (s, 3H), 2.7 (q, 2H), 3.5-3.65 (m, 4H), 3.72-3.77 (m, 1H), 3.85-3.91 (m, 1H), 4.34 (d, 2H), 5.04 (t, 1H), 6.4 (d, 1H), 6.89 (t, 1H), 7.04-7.12 (m, 2H), 7.18 (t, 1H), 7.78 (d, 1H)

Example 1.16

Synthesis of 2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-(2-methoxyethyl)-imidazo[1,2-a]pyridine-6-carboxamide



2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.15 g, 0.44 mmol), o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU) (0.14 g, 0.44 mmol) and 2-methoxyethylamin (0.11 g, 1.4 mmol) in methylene chloride (10 ml).

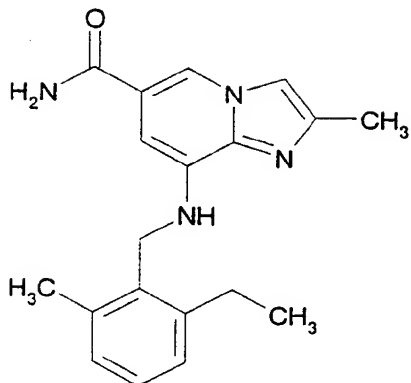
The title compound were prepared according to Example 1.14

Crystallization from hexane:ethylacetate. (Yield: 0.09 g, 53 %)

¹H-NMR (400 MHz, CDCl₃): δ 1.22 (t, 3H), 2.34 (s, 3H), 2.38 (s, 3H), 2.39 (s, 3H), 2.71 (q, 2H), 3.42 (s, 3H), 3.6-3.72 (m, 4H), 4.38 (d, 2H), 4.91 (t, 1H), 6.42 (s, 1H), 6.58 (t, 1H), 7.04-7.2 (m, 3H), 7.88 (s, 1H)

Example 1.17

Synthesis of 2-methyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide

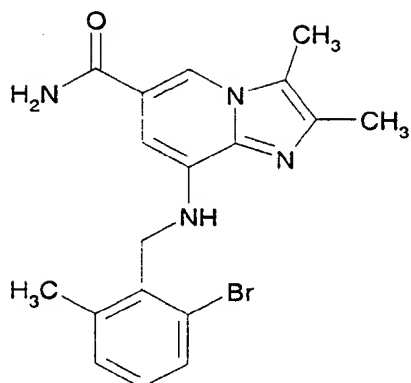


8-Amino-2-methylimidazo[1,2-a]pyridine-6-carboxamide (3.8 g, 20 mmol), 2-ethyl-6-methylbenzylchloride (2.8 g, 17 mmol), potassium carbonate (5.5 g, 40 mmol) and sodium iodide (0.1 g, 0.6 mmol) were added to dimethylformamide (75 ml) and the mixture was stirred at 50 °C for 4 h. and at room temperature for 48 h. The reaction mixture was filtered through silica gel and the gel was washed with methylene chloride. The solvents were evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using methylene chloride: methanol (9:1) as eluent. Crystallization from a mixture of methylene chloride and hexane gave 0.13 g (2 %) of the title compound.

¹H-NMR (400 MHz, CDCl₃): δ 1.15 (t, 3H), 2.31 (s, 6H), 2.64 (q, 2H), 4.32 (d, 2H), 4.89 (bs, 1H), 6.36 (s, 1H), 7.0-7.15 (m, 3H), 7.23 (s, 3H), 8.03 (s, 1H)

Example 1.18

Synthesis of 2,3-dimethyl-8-(2-bromo-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide

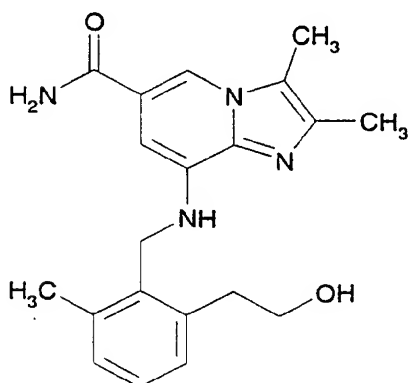


8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate (1.0 g, 5.0 mmol),
 2-bromo-6-methylbenzylchloride (45%)(3.0 g, 5.0 mmol) and diisopropylethylamin (2.2 g,
 17 mmol) were added to dimethylformamide (50 ml) and stirred at 50 °C for 48 h.
 Methylene chloride and water were added to the reaction mixture, the organic layer was
 separated, washed with saturated sodium chloride, dried (Na₂SO₄) and evaporated under
 reduced pressure. Purification of the residue twice by column chromatography on silica gel
 using methylene chloride: methanol (10:1) and ethylacetate as eluent gave 0.18 g (1 %) of
 the desired product.

¹H-NMR (300 MHz, CDCl₃): δ 2.28 (s, 3H), 2.30 (s, 3H), 2.36 (s, 3H), 4.48 (d, 2H), 5.0
 (bs, 1H), 6.05 (bs, 2H), 6.41 (d, 1H), 6.95-7.1 (m, 2H), 7.37 (d, 1H), 7.87 (d, 1H)

Example 1.19

Synthesis of 2,3-dimethyl-8-(2-(2-hydroxyethyl)-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide

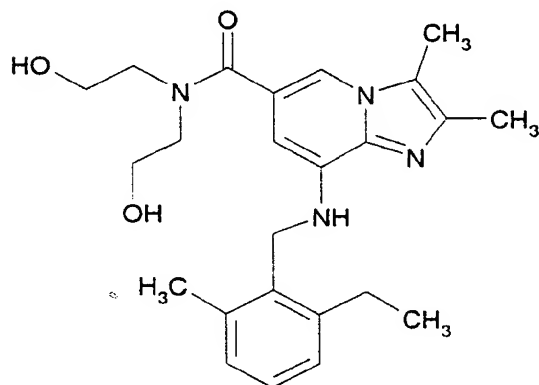


2,3-dimethyl-8-(2-(2-(benzyloxy)ethyl)-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide (0.13 g, 0.29 mmol), cyclohexene (1 ml), Pd(OH)₂ cat. (25 mg) were added to ethanol (5 ml) and the mixture was refluxed overnight. An additional amount of
5 cyclohexene (1 ml) and Pd(OH)₂ cat. (25 mg) were added and the mixture was refluxed for 4 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using methylene chloride: methanol (9:1) as eluent. Treating the residue with chloroform and filtration gave 0.1 g (99 %) of the title compound.

10 ¹H-NMR (400 MHz, CD₃OD): δ 2.29 (s, 3H), 2.40 (s, 3H), 2.42 (s, 3H), 2.94 (t, 2H), 3.74 (t, 2H), 4.47 (s, 2H), 6.83 (d, 1H), 7.11-7.20 (m, 3H), 8.12 (d, 1H)

Example 1.20

15 *Synthesis of 8-(2-ethyl-6-methylbenzylamino)-N,N-bis(2-hydroxyethyl)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide*



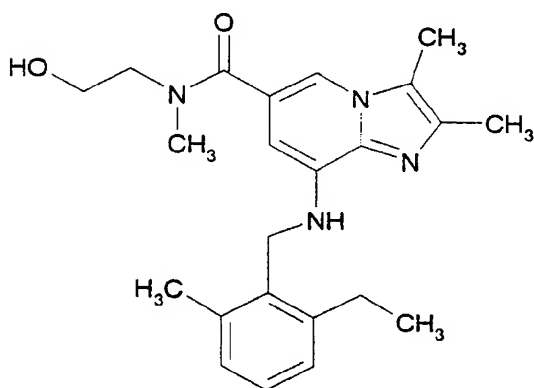
20 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.3 g, 0.88 mmol), o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU)(0.3 g, 0.94 mmol) and diethanolamine (0.2 g, 1.9 mmol) in methylene chloride (10 ml).

25 The title compound were prepared according to Example 1.14 (Yield: 0.19 g, 50 %)

¹H-NMR (400 MHz, CDCl₃): δ 1.2 (t, 3H), 2.3 (s, 3H), 2.35 (s, 3H), 2.4 (s, 3H), 2.7 (q, 2H), 3.65 (bs, 4H), 3.9 (bs, 4H), 4.35 (d, 2H), 4.95 (bs, 1H), 6.35 (s, 1H), 7.0-7.2 (m, 3H), 7.7 (s, 1H)

5 *Example 1.21*

Synthesis of 8-(2-ethyl-6-methylbenzylamino)-N-(2-hydroxyethyl)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide



10

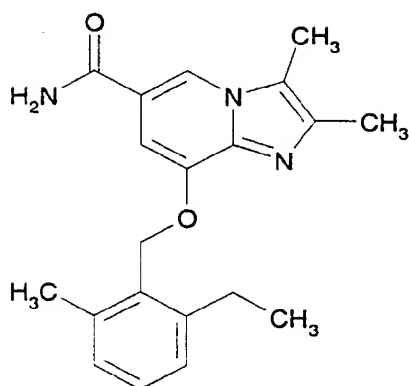
2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid (0.3 g, 0.88 mmol), o-Benzotriazol-1-yl-N,N,N',N'-Tetramethyluronium tetrafluoroborate (TBTU) (0.3 g, 0.94 mmol) and 2-(methylamino)ethanol (0.2 g, 2.66 mmol) in methylene
15 chloride (10 ml).

The title compound were prepared according to Example 1.14 (Yield: 0.25 g, 71 %)

¹H-NMR (600 MHz, CDCl₃): δ 1.2 (t, 3H), 2.25 (s, 6H), 2.35 (s, 3H), 2.7 (q, 2H), 3.15 (s,
20 3), 3.65 (bs, 2H), 3.9 (bs, 2H), 4.35 (d, 2H), 5.0 (bs, 1H), 6.25 (bs, 1H), 7.0-7.25 (m., 3H), 7.45 (bs, 1H)

Example 1.22

25 *Synthesis of 2,3-dimethyl-8-(2-ethyl-6-methylbenzyloxy)-imidazo[1,2-a]pyridine-6-carboxamide*



6-amino-5-(2-ethyl-6-methylbenzyloxy)nicotinamide (0.14 g, 0.49 mmol), 3-bromo-2-butanone (0.075 g, 0.49 mmol) and sodium bicarbonate (0.1 g, 1.2 mmol) was added to acetonitrile (3 ml) and was refluxed for 20 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using methylene chloride: methanol (9:1) as eluent. Crystallization from acetonitrile gave 0.058 g (35 %) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ 1.14 (t, 3H), 2.24 (s, 3H), 2.33 (s, 3H), 2.40 (s, 3H), 2.69 (q, 2H), 5.25 (s, 2H), 7.1-7.3 (m, 4H), 7.51 (bs, 1H), 8.08 (bs, 1H), 8.42 (s, 1H)

2. PREPARATION OF INTERMEDIATES

Example 2.1

Synthesis of methyl 6-amino-5-nitronicotinate

6-Chloro-5-nitronicotinoyl chloride (22.0 g, 0.1 mol) was cooled to +5°C. Methanol was added dropwise during 30 min and the reaction mixture was stirred for 60 min. The temperature was not allowed to raise over +10°C. Ammonium hydroxide (25%, 400 ml) was added dropwise to the reaction mixture and the mixture was stirred at room temperature for 20 h. The product was filtered off, washed with water and dried to give 9.0 g (45.9%) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 3.95 (s, 3H), 6.3 (bs, 1H), 8.0 (bs, 1H), 8.95 (s, 1H), 9.05 (s, 1H)

Example 2.2

5

Synthesis of methyl 5,6-diaminonicotinate

Methyl 6-amino-5-nitronicotinate (9.0 g, 46 mmol) and a small amount of Pd/C cat. were added to methanol (200 ml) and the mixture was hydrogenated at room temperature and atmospheric pressure until the uptake of hydrogen ceased. Following filtration through celite, the methanol was evaporated under reduced pressure to give the title compound, 7.0 g (92%).

¹H-NMR (300 MHz, CDCl₃): δ 3.3 (s, 2H), 3.9 (s, 3H), 4.75 (s, 2H), 7.45 (s, 1H), 8.35 (s, 1H)

15

Example 2.3

Synthesis of methyl 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate

20

Methyl 5,6-diaminonicotinate (0.9 g, 5.4 mmol) and 3-bromo-2-butanone (0.9 g, 6.0 mmol) were added to acetonitrile (30 ml) and refluxed for 24 h. Upon cooling some of the product was filtered off as hydrobromide salt. 20 ml of the filtrate was evaporated under reduced pressure and diethyl ether was added. More product was filtered off as hydrobromide salt. The salt was dissolved in methylene chloride and washed with a bicarbonate solution. The organic layer was separated, dried over Na₂SO₄ and evaporated under reduced pressure to give 0.7 g (59%) of the desired compound.

25

¹H-NMR (300 MHz, CDCl₃): δ 2.4 (s, 6H), 3.9 (s, 3H), 4.5 (s, 2H), 6.85 (s, 1H), 8.1 (s, 1H)

30

*Example 2.4**Synthesis of methyl 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylate*

Methyl 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate (0.7 g, 3.2 mmol), 2-ethyl-6-methylbenzylchloride (0.54 g, 3.2 mmol), potassium carbonate (0.9 g, 6.4 mmol) and a cat. amount of potassium iodide were added to acetonitrile (20 ml) and were refluxed for 6 h. Following filtration, the acetonitrile was evaporated under reduced pressure to give an oil. The oily residue was solved in methylene chloride and washed with water. The organic layer was separated, dried over Na₂SO₄ and evaporated under reduced pressure to give a solid. Purification by column chromatography on silica gel using methylene chloride : ethylacetate (10 : 1) as eluent gave 0.42 g (38%) of the title compound.

15

¹H-NMR (500 MHz, CDCl₃): δ 1.15 (t, 3H), 2.35 (s, 3H), 2.4 (s, 3H), 2.43 (s, 3H), 2.75 (q, 2H), 4.0 (s, 3H), 4.25 (d, 2H), 4.9 (bs, 1H), 6.8 (s, 1H), 7.05-7.2 (m, 3H), 8.1 (s, 1H)

Example 2.5

20

Synthesis of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylic acid

Methyl 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylate (0.4 g, 1.1 mmol) was added to a mixture of 1,4-dioxane (6 ml) and 2 M NaOH (6 ml) and was refluxed for 30 min. The dioxane was evaporated under reduced pressure and the aqueous solution was made acidic by addition of 2 M HCl. The acidic aqueous was basified by the addition of a saturated bicarbonate solution and the solid that formed was isolated by filtration to give 0.35 g (91%) of the title compound.

30

¹H-NMR (400 MHz, DMSO-d₆): δ 1.15 (t, 3H), 2.2 (s, 3H), 2.35 (s, 6H), 2.7 (q, 2H), 4.35 (d, 2H), 4.65 (t, 1H), 6.8 (s, 1H), 7.05-7.2 (m, 3H), 7.95 (s, 1H)

Example 2.6

5

Synthesis of ethyl 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate

Ethyl 5,6-diaminonicotinate (1.4 g, 7.7 mmol) and 3-bromo-2-butanone (1.16 g, 7.2 mmol) were added to 1,2-dimethoxyethane (50 ml) and refluxed for 20 h. The solvent was
10 evaporated under reduced pressure and the residue was dissolved in methylene chloride. The methylene chloride solution was washed with saturated sodium bicarbonate and dried (Na₂SO₄). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using methylene chloride : methanol (10 : 1) as eluent to give 0.3 g (17 %) of the title compound.

15

¹H-NMR (300 MHz, CDCl₃): δ 1.4 (t, 3H), 2.4 (s, 6H), 4.35 (q, 2H), 4.6 (s, 2H), 6.75 (s, 1H), 8.2 (s, 1H)

Example 2.7

20

Synthesis of ethyl 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxylate

Ethyl 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxylate (0.7 g, 3.0 mmol), 2-ethyl-6-methylbenzylchloride (0.5 g, 3.0 mmol), sodium carbonate (0.64 g, 6.0 mmol) and
25 a cat. amount of potassium iodide were added to acetone (50 ml) and were refluxed for 20 h. Following filtration, the acetone was evaporated under reduced pressure to give an oil. The oily product was purified by column chromatography on silica gel using diethyl ether : petroleum ether (1:1) as eluent to give 0.12 g (9%) of the title product.

30

¹H-NMR (500 MHz, CDCl₃): δ 1.25 (t, 3H), 1.5 (t, 3H), 2.35 (s, 3H), 2.42 (s, 3H), 2.44 (s, 3H), 2.75 (q, 2H), 4.45-4.5 (m, 4H), 4.9 (bs, 1H), 6.8 (s, 1H), 7.05-7.2 (m, 3H), 8.1 (s, 1H)

Example 2.8

5

Synthesis of 6-amino-5-nitronicotinamide

A solution of 6-chloro-5-nitronicotinoyl chloride (38 g, 0.2 mol) in tetrahydrofuran (500 ml) was stirred at +5°C and ammonia was bubbled into the solution. After 1 h the reaction mixture was allowed to warm to room temperature and ammonia was bubbled into the solution for additional 2.5 h. The reaction mixture was stirred at room temperature for 20 h. The solids were removed by filtration, washed thoroughly with water and were dried under reduced pressure to give 18.5 g (51%) of the title compound.

15 ¹H-NMR (400 MHz, DMSO-d₆): δ 7.4 (s, 1H), 8.05 (s, 1H), 8.3 (s, 2H), 8.8 (s, 2H)

Example 2.9

Synthesis of 5,6-diaminonicotinamide

20

A suspension of 6-amino-5-nitronicotinamide (18 g, 99 mmol) and a cat. amount of Pd/C in methanol (600 ml) and the mixture was hydrogenated at room temperature and atmospheric pressure until the uptake of hydrogen ceased. Following filtration through celite, the methanol was evaporated under reduced pressure to give the title compound, 14.5 g (96%).

25

¹H-NMR (300 MHz, DMSO-d₆): δ 5.0 (bs, 2H), 6.1 (bs, 2H), 6.9 (bs, 1H), 7.15 (s, 1H), 7.55 (bs, 1H), 7.9 (s, 1H)

30 Example 2.10

Synthesis of 8-amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide

5,6-Diaminonicotinamide (12.5 g, 82 mmol), 3-bromo-2-butanon (13.6, 90 mmol) and
5 acetonitrile (150 ml) were refluxed for 20 h. Additional 3-bromo-2-butanon (4.0 g, 26.5
mmol) was added and the reaction mixture was refluxed for 5 h. Upon cooling the solids
were removed by filtration. The solids were added to methylene chloride (150 ml),
methanol (150 ml) and potassium carbonate (22 g, 160 mmol) and were stirred for 30 min.
The solids were removed by filtration and evaporation of the solvents under reduced
10 pressure gave an oily residue. Purification by column chromatography on silica gel eluting
with methylene chloride : methanol (5:1) gave 3.3 g (20%) of the title compound.

¹H-NMR (400 MHz, DMSO-d₆): δ 2.25 (s, 3H), 2.35 (s, 3H), 5.6 (s, 2H), 6.65 (s, 1H),
7.15 (bs, 1H), 7.85 (bs, 1H), 8.05 (s, 1H)

15

Example 2.11

Synthesis of ethyl 8-amino-6-(aminocarbonyl)-2-methylimidazo[1,2-a]pyridine-3-carboxylate

20

5,6-Diaminonicotinamide (2.0 g, 13.4 mmol), ethyl-2-chloroacetoacetate (2.38 g, 14.4
mmol) and ethanol (40 ml) were refluxed for 20 h. The precipitate was isolated by filtration
and washed with ethanol and diethyl ether. The solids were suspended in water, basified
with a sodium hydroxide solution and isolated by filtration. Washing the solids with water
25 and diethyl ether gave 0.42 g (12%) of the desired product.

30

Example 2.12

¹H-NMR (500 MHz, DMSO-d₆): δ 1.4 (t, 3H), 2.6 (s, 3H), 4.35 (q, 2H), 5.95 (bs, 2H), 6.9
(s, 1H), 7.35 (bs, 1H), 8.0 (bs, 1H), 9.0 (s, 1H)

Synthesis of ethyl 6-(aminocarbonyl)-8-(2-ethyl-6-methylbenzylamino)-2-methylimidazo[1,2-a]pyridine-3-carboxylate

Ethyl 8-amino-6-(aminocarbonyl)-2-methylimidazo[1,2-a]pyridine-3-carboxylate (0.41 g, 1.6 mmol), 2-ethyl-6-methylbenzylchloride, sodium carbonate (0.7 g, 6.6 mmol), sodium iodide (0.15 g, 1.0 mmol) and acetone (20 ml) were refluxed for 44 h. Methylene chloride was added and the solids were removed by filtration. The filtrate was evaporated under reduced pressure and purification of the residue by column chromatography on silica gel eluting with methylene chloride : methanol (100 : 4) gave 0.35 g (56%) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 1.25 (t, 3H), 1.45 (t, 3H), 2.35 (s, 3H), 3.65 (s, 3H), 2.7 (q, 2H), 4.4-4.45 (m, 4H), 5.0 (t, 1H), 6.95 (s, 1H), 7.0-7.2 (m, 3H), 9.2 (s, 1H)

Example 2.13

Synthesis of 8-amino-2-methylimidazo[1,2-a]pyridine-6-carboxamide mesylate

5,6-diaminonicotinamide (10 g, 66 mmol), chloroacetone (6.1 g, 66 mmol) and sodium bicarbonate (11.2 g, 132 mmol) were added to dimethylformamide (200 ml) and the mixture was stirred for 72 h. at room temperature. Most of the solvent was evaporated under reduced pressure and methanesulfonic acid (6 g, 63 mmol) was added. More solvent was evaporated under reduced pressure and ethanol was added to the residue. Upon warming the mixture to 60 °C. the product crysstallized as salt and was filtered off to give 6 g (32 %) of the title compound.

¹H-NMR (400 MHz, CDCl₃): δ 2.3 (s, 6H), 7.25 (s, 1H), 7.4 (s, 1H), 7.6 (s, 1H), 7.75 (s, 1H), 7.85 (s, 1H), 7.9 (s, 1H), 8.15 (s, 1H), 8.6 (s, 1H)

Example 2.14

Synthesis of 1-bromo-2-isopropyl-6-methylbenzene

2-isopropyl-6-methylanilin (14.9 g, 0.1 mol) was solved in conc hydrobromic acid (40 ml) and the mixture was cooled to 5 °C. Sodium nitrite (7.0 g, 0.1 mol) in water (15 ml) was added so that the temperature was below 10 °C. A solution of copper(I)bromide in conc
5 hydrobromic acid (10 ml) was added to the reaction mixture and the temperature was allowed to raise to room temperature. The mixture was stirred for 1h. at room temperature and 30 min at 40 °C Hexane was added and the organic layer was separated and evaporated under reduced pressure. Purification by column chromatography on silica gel using hexane as eluent gave 6.9 g (32 %) of the title compound as an oil.

10 ¹H-NMR (300 MHz,CDCl₃): δ 1.23 (d, 6H), 2.43 (s, 3H), 3.4-3.55 (m, 1H), 7.05-7.2 (m, 3H)

Example 2.15

15 *Synthesis of 2-isopropyl-6-methylbenzaldehyd*

To a solution of 1-bromo-2-isopropyl-6-methylbenzene (6.9 g, 32.4 mmol) in diethyl ether (50 ml) was added magnesium turnings (0.9 g, 37 mmol) and the mixture was refluxed in
20 nitrogen atmosphere until the reaction was started and was then stirred overnight at room temperature. Dimethylformamide (4 ml) was added dropwise during 10 min. and the mixture was stirred for 30 min. Saturated ammoniumchloride solution (30 ml) was added and the mixture was stirred for 1h. The organic layer was separated, filtrated and evaporated under reduced pressure. Purification by column chromatography on silica gel
25 using hexane:methylene chloride (3:2) as eluent gave 1.75 g (33 %) of the title compound .

¹H-NMR (500 MHz,CDCl₃): δ 1.25 (d, 6H), 2.55 (s, 3H), 3.7-3.8 (m, 1H), 7.1-7.4 (m, 3H), 10.65 (s, 1H)

30 *Example 2.16*

Synthesis of 2-isopropyl-6-methylbenzylalcohol

To a solution of 2-isopropyl-6-methylbenzaldehyd (1.75 g, 10.8 mmol) in methanol (15 ml) was added sodium borohydride (0.35 g, 9.5 mmol) and the mixture was stirred 1 h. at room temperature. The solvent was evaporated under reduced pressure and to the residue was added hexane and water. The organic layer was separated and evaporated under reduced pressure to give 1.73 g (98 %) of the title compound as an oil.

$^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 1.25 (d, 6H), 2.45 (s, 3H), 3.3-3.4 (m, 1H), 4.8 (s, 2H), 7.05- 7.2 (m, 3H)

Example 2.17

Synthesis of 2-isopropyl-6-methylbenzylchloride

To a solution of 2-isopropyl-6-methylbenzylalcohol (1.7 g, 10.4 mmol) in methylene chloride (20 ml) was added thionyl chloride (1.7 g, 14 mmol) and the reaction was stirred for 1 h. at room temperature. The solvent was evaporated under reduced pressure and the residue was filtrated through silica gel using methylenechloride as eluent. The solvent was evaporated under reduced pressure to give 1.83 g (96 %) of the title compound as an oil.

$^1\text{H-NMR}$ (500 MHz, CDCl_3): δ 1.25 (d, 6H), 2.45 (s, 3H), 3.25-3.35 (m, 1H), 4.75 (s, 2H), 7.05-7.25 (m, 3H)

Example 2.18

Synthesis of 2-bromo-6-methylbenzylbromide

A mixture of 3-bromo-o-xylene (15 g, 81 mmol), N-bromo succinimid (15.1 g, 85.1 mmol), dibenzoylperoxid (0.65 g) and tetrachloromethane (150 ml) was refluxed for 5 hours. After filtration the filtrate was washed with sodium hydrogensulfite and water. The organic layer was dried over sodium sulfate and evaporated *in vacuo*. Chromatography (SiO_2) (petroleum ether: ethyl acetate, 100:4) gave a 16.8 g fraction of a mixture containing 45 % of the title compound. This mixture was used without further purification.

¹H-NMR (300 MHz, CDCl₃): δ 2.5 (s, 3H), 4.65 (s, 2H), 7.05-7.45 (m, 3H)

Example 2.19

5 *Synthesis of 2-(2-bromo-3-methylphenyl)acetonitril*

2-bromo-1-(bromomethyl)-3-methylbenzene (15 g, 0.057 mmol) and potassium cyanide (9.6 g, 0.148 mol) were added to dimethylformamide (75 ml) and stirred at 90 °C overnight. The solvent was evaporated under reduced pressure and the residue partitioned
10 between water (150 ml) and methylene chloride. The aqueous layer was extracted twice with methylene chloride, the organic extracts was separated, washed twice with water and was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using heptane:methylene chloride (3:7) as eluent gave 8.0 g (67 %) of the title compound.

15

¹H-NMR (500 MHz, CDCl₃): δ 2.44 (s, 3H), 3.86 (s, 2H), 7.22-7.37 (m, 3H)

Example 2.20

20 *Synthesis of 2-(2-bromo-3-methylphenyl)acetic acid*

2-(2-bromo-3-methylphenyl)acetonitril (8.0 g, 0.038 mol) was added to a mixture of water (60 ml) and sulfuric acid (50 ml) and the mixture was refluxed overnight. After cooling to room temperature water (200 ml) was added and the mixture was extracted twice with
25 methylene chloride. The methylene chloride extracts were combined, washed twice with water, dried and evaporated under reduced pressure to give 7.9 g (90.8 %) of the title compound.

30

¹H-NMR (400 MHz, CDCl₃): δ 2.42 (s, 3H), 3.86 (s, 2H), 7.09-7.18 (m, 3H)

Example 2.21

Synthesis of ethyl 2-(2-bromo-3-methylphenyl)acetate

2-(2-bromo-3-methylphenyl)acetic acid (7.9 g, 0.034 mol) and sulfuric acid (0.1 ml) were added to ethanol (25 ml) and the mixture was refluxed overnight. The solvent was evaporated and to the residue was added saturated sodium carbonate. The aqueous solution was extracted twice with diethyl ether, the organic extracts were combined, washed twice with water, dried and evaporated under reduced pressure to give the desired product as an oil. (8.5 g, 97.7%).

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.24 (t, 3H), 2.40 (s, 3H), 3.78 (s, 3H), 4.16 (q, 2H), 7.06-7.14 (m, 3H)

Example 2.22

Synthesis of 2-(2-bromo-3-methylphenyl)-1-ethanol

LiAlH_4 (3.1 g, 0.083 mol) was suspended in dry tetrahydrofuran (100 ml) in argon atmosphere. Ethyl 2-(2-bromo-3-methylphenyl)acetate (8.5 g, 0.033 mol) dissolved in dry tetrahydrofuran (50 ml) was added and the mixture was stirred at room temperature for 4 h. The mixture was cooled on ice and 3.1 ml of water was added dropwise, followed by 3.1 ml of 15% sodium hydroxide and then 9.3 ml of water. After 15 h. the solids were removed by filtration and washed thoroughly with tetrahydrofuran. The filtrate was removed under reduced pressure. Purification of the residue by filtering through silica gel using methylene chloride : methanol (9:1) as eluent gave 7.0 g (98.6 %) of the title compound as an oil.

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 2.39 (s, 3H), 3.00 (t, 2H), 3.81 (t, 2H), 7.04-7.10 (m, 3H)

Example 2.23

Synthesis of benzyl 2-bromo-3-methylphenethyl ether

Sodium hydride (50 % in oil) (1.7 g, 0.036 mol) was suspended in dry tetrahydrofuran (75 ml) in argon atmosphere. 2-(2-bromo-3-methylphenyl)-1-ethanol (7.0 g, 0.033 mol) dissolved in tetrahydrofuran (25 ml) was added dropwise during 30 min at room temperature. Benzyl bromide (6.2 g, 0.036 mol) was added and the reaction mixture was stirred at room temperature over night. Water (1.0 ml) was added carefully and the solvent was evaporated

under reduced pressure. The residue was partitioned between water and diethyl ether and the water layer was extracted twice with diethyl ether. The ether extracts were combined, washed twice with water, and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using heptane:methylene chloride (7:3) as eluent gave 7.5 g (74.3 %) of the title compound.

¹H-NMR (400 MHz, CDCl₃): δ 2.38 (s, 3H), 3.10 (t, 2H), 3.69 (t, 2H), 4.51 (s, 2H), 7.04-7.08 (m, 3H), 7.21-7.30 (m, 5H)

Example 2.24

Synthesis of 2-[2-(benzyloxy)ethyl]-6-methylbenzaldehyde

To a solution of benzyl 2-bromo-3-methylphenethyl ether (3.2 g, 0.0105 mol) in dry tetrahydrofuran in a nitrogen atmosphere at -65 °C was added tert-butyllithium (1.7 M in pentane) (10.5 ml, 0.018 mol) and the mixture was stirred at -20 °C for 30 min. Dimethylformamide (1.5 g, 0.021 mol) was added dropwise at -65 °C and the mixture was stirred at -20 °C for 30 min and at room temperature for 1 h. To the solution was water added carefully and 2M HCl to make it acidic and the mixture was stirred for 30 min. To the mixture was added diethyl ether (50 ml), the organic layer was separated, washed with saturated sodium carbonate and water. The organic layer was separated, dried and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using heptane:methylene chloride (2:8) as eluent gave 1.0 g (38.5 %) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 2.55 (s, 3H), 3.23 (t, 2H), 3.66 (t, 2H), 4.46 (s, 2H), 7.05-7.31 (m, 8H), 10.54 (s, 1H)

Example 2.25

Synthesis of 8-((2-[2-(benzyloxy)ethyl]-6-methylbenzyl)amino)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide

To a solution of 8-Amino-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide mesylate 1.4 g (0.0038 mol) in methanol (20 ml) in a nitrogen atmosphere was added zinc chloride (1.0

g, 0.0039 mol) solved in methanol(10 ml) and the mixture was stirred for 30 min. To the mixture were added 2-[2-(benzyloxy)ethyl]-6-methylbenzaldehyde (1.0 g, 0.0039 mol) and sodium cyano borohydride (0.48 g, 0.0076 mol) and the mixture was refluxed overnight. The reaction mixture was cooled to room temperature, triethylamine (4 ml) was added, the mixture was stirred for 30 min, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using methylene chloride:methanol (9:1) as eluent. The residue was solved in diethyl ether, treated with diethyl ether/HCl and the precipitated product as HCl salt was filtered off. The salt was solved in methylene chloride and washed with saturated sodium carbonate. The organic layer was separated, washed with water, dried and evaporated under reduced pressure to give 0.13 g (7.7 g) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 2.31 (s, 3H), 2.33 (s, 3H), 2.34 (s, 3H), 2.98 (t, 2H), 3.66 (t, 2H), 4.37 (d, 2H), 4.46 (s, 2H), 5.02 (bs, 1H), 6.29 (bs, 2H), 6.47 (s, 1H), 7.03-7.26 (m, 8H), 7.91 (s, 1H)

Example 2.26

Synthesis of 2-ethyl-6-methylbenzyl 5-(2-ethyl-6-methylbenzyloxy)-6-nitronicotinate

5-hydroxy-6-nitronicotinic acid (1 g, 5 mmol), 2-ethyl-6-methylbenzylchloride (1.85 g, 11 mmol), N,N-diisopropylamine (1.75 g, 14 mmol) and tetrabutylammonium iodide (0.1 g) was added to acetonitrile (10 ml) and was refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue was solved in methylene chloride and washed with water. The organic layer was separated, dried and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using n-hexane:methylene chloride (1:1) as eluent gave 0.7 g (29 %) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 1.2 (t, 3H), 1.25 (t, 3H), 2.35 (s, 3H), 2.45 (s, 3H), 2.7 (q, 2H), 2.8 (q, 2H), 5.25 (s, 2H), 5.55 (s, 2H), 7.05-7.3 (m, 6H), 8.2 (s, 1H), 8.65 (s, 1H)

Example 2.27

Synthesis of 6-amino-5-(2-ethyl-6-methylbenzyloxy)nicotinamide

2-ethyl-6-methylbenzyl 5-(2-ethyl-6-methylbenzyloxy)-6-nitronicotinate (0.7 g, 2 mmol) was added to a solution of ammonia in methanol (5-10 %)(40 ml) and the mixture was stirred at 35 °C for 96 h. The solvent was evaporated under reduced pressure. Purification of the residue twice by column chromatography on silica gel using ethylacetate:methylene chloride (1:1) and methanol:methylene chloride (1:9) as eluent gave 0.14 g (31 %) of the title compound.

¹H-NMR (500 MHz, CDCl₃): δ 1.21 (t, 3H), 1.87 (s, 2H), 2.37 (s, 3H), 2.72 (q, 2H), 5.11 (s, 2H), 5.99 (bs, 2H), 7.1-7.3 (m, 3H), 7.67 (d, 1H), 8.09 (d, 1H)

BIOLOGICAL TESTS

1. In vitro experiments

Acid secretion inhibition in isolated rabbit gastric glands

Inhibiting effect on acid secretion *in vitro* in isolated rabbit gastric glands was measured as described by Berglinde et al. (1976) Acta Physiol. Scand. 97, 401-414.

Determination of H⁺, K⁺-ATPase activity

Membrane vesicles (2.5 to 5 µg) were incubated for 15 min at +37°C in 18 mM Pipes/Tris buffer pH 7.4 containing 2 mM MgCl₂, 10 mM KCl and 2 mM ATP. The ATPase activity was estimated as release of inorganic phosphate from ATP, as described by LeBel et al. (1978) Anal. Biochem. 85, 86-89.

2. In vivo experiments

Inhibiting effect on acid secretion in female rats

Female rats of the Sprague-Dawley strain are used. They are equipped with cannulated fistulae in the stomach (lumen) and the upper part of the duodenum, for collection of

gastric secretions and administration of test substances, respectively. A recovery period of 14 days after surgery is allowed before testing commenced.

Before secretory tests, the animals are deprived of food but not water for 20 h. The stomach is repeatedly washed through the gastric cannula with tap water (+37°C), and 6 ml Ringer-Glucose given subcutaneously. Acid secretion is stimulated with infusion during 2.5-4 h (1.2 ml/h, subcutaneously) of pentagastrin and carbachol (20 and 110 nmol/kg-h, respectively), during which time gastric secretions are collected in 30-min fractions. Test substances or vehicle are given either at 60 min after starting the stimulation (intravenous and intraduodenal dosing, 1 ml/kg), or 2 h before starting the stimulation (oral dosing, 5 ml/kg, gastric cannula closed). The time interval between dosing and stimulation may be increased in order to study the duration of action. Gastric juice samples are titrated to pH 7.0 with NaOH, 0.1 M, and acid output calculated as the product of titrant volume and concentration.

Further calculations are based on group mean responses from 4-6 rats. In the case of administration during stimulation; the acid output during the periods after administration of test substance or vehicle are expressed as fractional responses, setting the acid output in the 30-min period preceding administration to 1.0. Percentage inhibition is calculated from the fractional responses elicited by test compound and vehicle. In the case of administration before stimulation; percentage inhibition is calculated directly from acid output recorded after test compound and vehicle.

Bioavailability in rat

Adult rats of the Sprague-Dawley strain are used. One to three days prior to the experiments all rats are prepared by cannulation of the left carotid artery under anaesthesia. The rats used for intravenous experiments are also cannulated in the jugular vein (Popovic (1960) J. Appl. Physiol. 15, 727-728). The cannulas are exteriorized at the nape of the neck.

Blood samples (0.1 - 0.4 g) are drawn repeatedly from the carotid artery at intervals up to 5.5 hours after given dose. The samples are frozen until analysis of the test compound.

5 Bioavailability is assessed by calculating the quotient between the area under blood/plasma concentration (AUC) curve following (i) intraduodenal (i.d.) or oral (p.o.) administration and (ii) intravenous (i.v.) administration from the rat or the dog, respectively.

10 The area under the blood concentration vs. time curve, AUC, is determined by the log/linear trapezoidal rule and extrapolated to infinity by dividing the last determined blood concentration by the elimination rate constant in the terminal phase. The systemic bioavailability (F%) following intraduodenal or oral administration is calculated as $F(\%) = (AUC \text{ (p.o. or i.d.)} / AUC \text{ (i.v.)}) \times 100$.

Inhibition of gastric acid secretion and bioavailability in the conscious dog.

15

Labrador retriever or Harrier dogs of either sex are used. They are equipped with a duodenal fistula for the administration of test compounds or vehicle and a cannulated gastric fistula or a Heidenhaim-pouch for the collection of gastric secretion.

20 Before secretory tests the animals are fasted for about 18 h but water is freely allowed. Gastric acid secretion is stimulated for up to 6.5 h infusion of histamine dihydrochloride (12 ml/h) at a dose producing about 80% of the individual maximal secretory response, and gastric juice collected in consecutive 30-min fractions. Test substance or vehicle is given orally, i.d. or i.v., 1 or 1.5 h after starting the histamine infusion, in a volume of 0.5 ml/kg
25 body weight. In the case of oral administration, it should be pointed out that the test compound is administered to the acid secreting main stomach of the Heidenham-pouch dog.

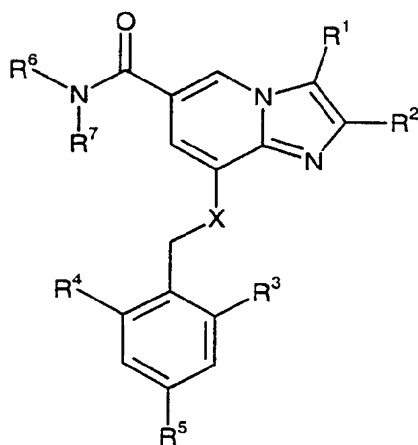
30 The acidity of the gastric juice samples are determined by titration to pH 7.0, and the acid output calculated. The acid output in the collection periods after administration of test substance or vehicle are expressed as fractional responses, setting the acid output in the

fraction preceding administration to 1.0. Percentage inhibition is calculated from fractional responses elicited by test compound and vehicle.

5 Blood samples for the analysis of test compound concentration in plasma are taken at intervals up to 4 h after dosing. Plasma is separated and frozen within 30 min after collection and later analyzed. The systemic bioavailability (F%) after oral or i.d. administration is calculated as described above in the rat model.

CLAIMS

1. A compound of the formula I



I

or a pharmaceutically acceptable salt thereof, wherein

R^1 is

- (a) H,
- (b) CH_3 , or
- (c) CH_2OH ;

R^2 is

- (a) CH_3
- (b) CH_2CH_3

R^3 is (a) H

- (b) C_1 - C_6 alkyl,
- (c) hydroxylated C_1 - C_6 alkyl
- (d) halogen

R^4 is

- (a) H,
- (b) C_1 - C_6 alkyl,

- (c) hydroxylated C₁-C₆ alkyl, or
(d) halogen;

R⁵ is

- 5 (a) H, or
(b) halogen;

R⁶, R⁷ are the same or different

- 10 (a) H,
(b) C₁-C₆ alkyl;
(c) hydroxylated C₁-C₆ alkyl
(d) C₁-C₆ alkoxy-substituted C₁-C₆ alkyl

15

X is

- (a) NH, or
(b) O.

- 20 2. A compound according to claim 1 wherein R¹ is CH₃ or CH₂OH; R², R³ and R⁴
independently are CH₃ or CH₂CH₃; and R⁵ is H, Br, Cl, or F.

3. The compound according to claim 1 or 2 being

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-propyl-imidazo[1,2-a]pyridine-6-
25 carboxamide,

8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-
6-carboxamide,

2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-
6-carboxamide,

30 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-
carboxamide,

8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-
carboxamide,

8-(2-ethyl-6-methylbenzylamino)-N,N,2,3-tetramethylimidazo[1,2-a]pyridine-6-carboxamide,

2,3-dimethyl-8-(2,6-dimethylbenzyl-amino)-imidazo[1,2-a]pyridine-6-carboxamide,

N-[2-(dimethylamine)-2-oxoethyl]-8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide

2,3-dimethyl-8-(2-ethyl-4-fluoro-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate,

2,3-dimethyl-8-(2-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide,

2,3-dimethyl-8-(2,6-dimethyl-4-fluoro-benzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate,

2,3-dimethyl-8-(2-methyl-6-isopropylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate,

2,3-dimethyl-8-(2,6-diethyl-benzylamino)-imidazo[1,2-a]pyridine-6-carboxamide,

2,3-dimethyl-8-(2-ethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide,

2,3 dimethyl-8-(2-ethyl-6-methyl-benzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-6-carboxamide,

N-(2,3-dihydroxypropyl)-2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-[1,2-a]pyridine-6-carboxamide,

2,3 dimethyl-8-(2-ethyl-6-methyl-benzylamino)-N-(2-methoxyethyl)-imidazo[1,2-a]pyridine-6-carboxamide,

2-methyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide,

2,3-dimethyl-8-(2-bromo-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide,

2,3-dimethyl-8-(2-(2-hydroxyethyl)-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide,

8-(2-ethyl-6-methylbenzylamino)-N,N-bis(2-hydroxyethyl)-2,3-dimethylimidazo[1,2-a]pyridine-6-carboxamide,

8-(2-ethyl-6-methylbenzylamino)-N-(2-hydroxyethyl)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-carboxamide,

2,3-dimethyl-8-(2-ethyl-6-methylbenzyloxy)-imidazo[1,2-a]pyridine-6-carboxamide
or

a pharmaceutically acceptable salt thereof.

4. The compound according to claim 1 or 2 being;

8-(2-ethyl-6-methylbenzylamino)-3-hydroxymethyl-2-methylimidazo[1,2-a]pyridine-
5 6-carboxamide,

2,3-dimethyl-8-(2,6-dimethylbenzylamino)-N-hydroxyethyl-imidazo[1,2-a]pyridine-
6-carboxamide,

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-
carboxamide,

10 8-(2-ethyl-6-methylbenzylamino)-N,2,3-trimethylimidazo[1,2-a]pyridine-6-
carboxamide,

2,3-dimethyl-8-(2,6-dimethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide,

2,3-dimethyl-8-(2-ethyl-4-fluoro-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-
carboxamide,

15 2,3-dimethyl-8-(2,6-dimethyl-4-fluoro-benzylamino)-imidazo[1,2-a]pyridine-6-
carboxamide,

2,3-dimethyl-8-(2,6-diethylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide,

2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-hydroxyethyl-imidazo[1,2-
a]pyridine-6-carboxamide,

20 2,3 dimethyl-8-(2-ethyl-6-methylbenzylamino)-N-(2-methoxyethyl)-imidazo[1,2-
a]pyridine-6-carboxamide,

or

a pharmaceutically acceptable salt thereof.

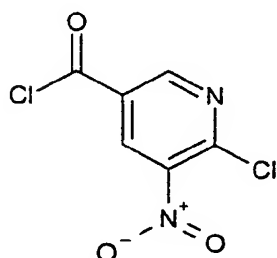
25 5. A compound according to any of claims 1-4 as a hydrochloride or mesylate salt.

6. Products containing at least one compound according to any of claims 1-4 and at least
one antimicrobial agent as a combined preparation for simultaneous, separate or
sequential use in the prevention or treatment of gastrointestinal inflammatory diseases.

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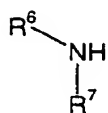
7. Products containing at least one compound according to any of claims 1-4 and at least one proton pump inhibitor as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of gastrointestinal inflammatory diseases.
8. A process for the preparation of a compound according to any one of claims 1 to 5, wherein X is NH, comprising

(a) reacting a compound of the Formula II



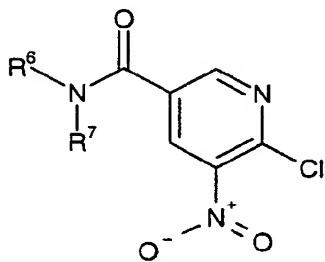
II

with a compound of the Formula III



III

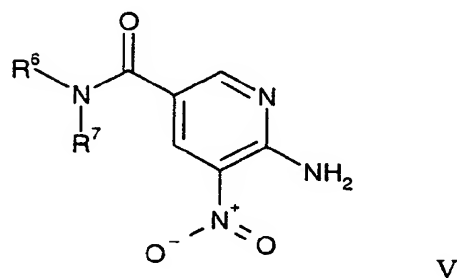
wherein R^6 and R^7 are as defined in claim 1, in an inert solvent, to a compound of the Formula IV,



IV

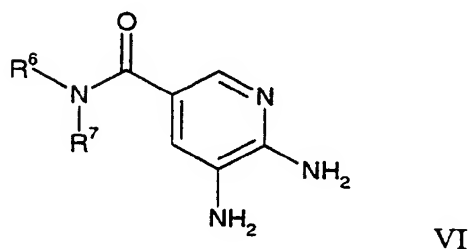
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- (b) reacting a compound of the Formula IV wherein R^6 and R^7 are as defined in claim 1, with ammonia in an inert solvent to a compound of the Formula V



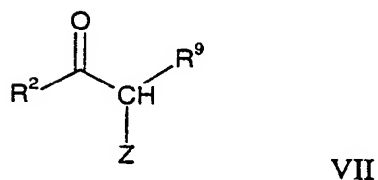
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- (c) reducing a compound of the Formula V wherein R^6 and R^7 are as defined in claim 1 in an inert solvent under standard conditions to a compound of the Formula VI



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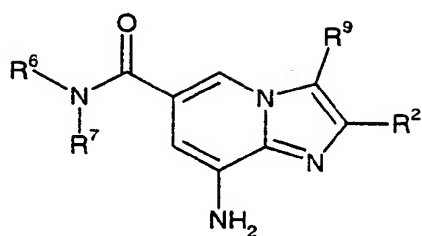
- (d) reacting a compound of the Formula VI wherein R^6 and R^7 are as defined in claim 1 with a compound of Formula VII



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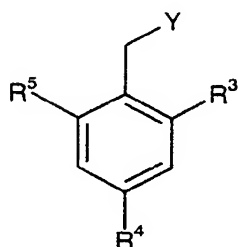
wherein R^2 is as defined in claim 1, Z is a leaving group and R^9 represent H, CH_3 or an ester group, in an inert solvent with or without a base to a compound of the Formula VIII

62



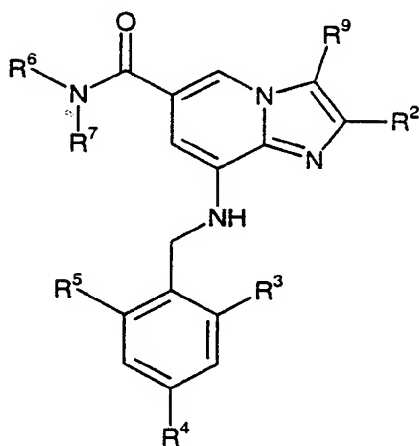
VIII

(e) reacting a compound of the Formula VIII wherein R^6 , R^7 and R^2 are as defined in claim 1, and R^9 is H, CH_3 or an ester group with a compound of Formula IX



IX

wherein R^3 , R^4 , and R^5 are as defined in claim 1, and Y is a leaving group in an inert solvent with or without a base, to a compound of the Formula X

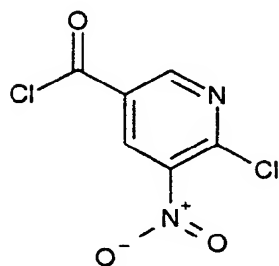


X

(f) reducing a compound of Formula X wherein R^9 is an ester group in an inert solvent to a compound of the Formula I wherein R^1 is CH_2OH and X is NH.

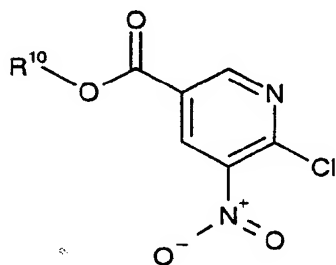
9. A process for the preparation of a compound according to any one of claims 1 to 5, wherein X is NH and R¹ is H or CH₃, comprising

5 (a) reacting a compound of the Formula II



II

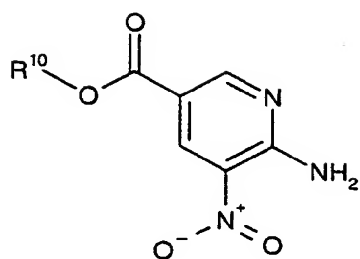
10 with an alcohol compound of the general formula R¹⁰-OH, wherein R¹⁰ is an alkyl group under standard conditions, to a compound of the Formula XI



XI

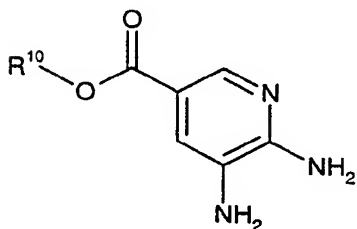
15 (b) reacting a compound of the Formula XI wherein R¹⁰ is an alkyl group, with ammonia in an inert solvent under standard conditions to a compound of the Formula XII

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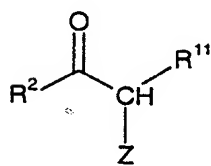
XII

(c) reducing a compound of the Formula XII wherein R^{10} is an alkyl group in an inert solvent under standard conditions to a compound of the Formula XIII



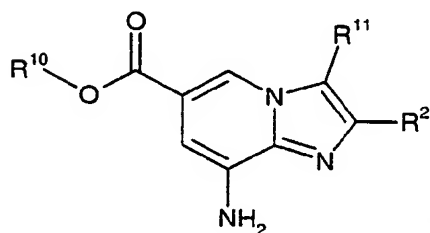
XIII

(d) reacting a compound of the Formula XIII wherein R^{10} is an alkyl group with a compound of Formula XIV



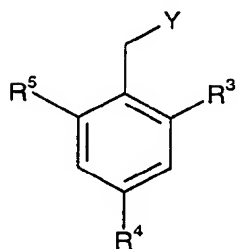
XIV

wherein R^2 is as defined in claim 1, Z is a leaving group and R^{11} represent H or CH_3 , in an inert solvent with or without a base to a compound of the Formula XV



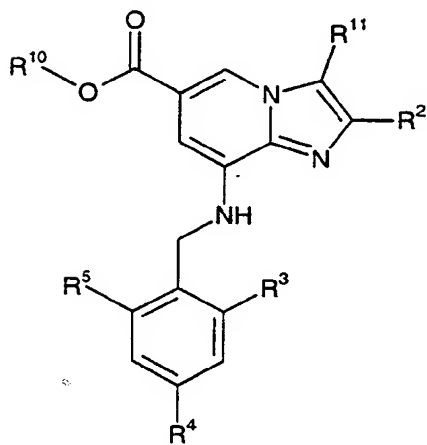
XV

(e) reacting a compound of the Formula XV wherein R^{10} is an alkyl group, R^2 are as defined in claim 1 and R^{11} is H or CH_3 with a compound of Formula IX



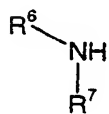
IX

wherein R^3 , R^4 , and R^5 are as defined in claim 1 and Y is a leaving group in an inert solvent with or without a base to a compound of the Formula XVI



XVI

(f) reacting a compound of Formula XVI wherein R^2 , R^3 , R^4 and R^5 are as defined in claim 1, R^{10} is an alkyl group and R^{11} is H or CH_3 with a compound of Formula III

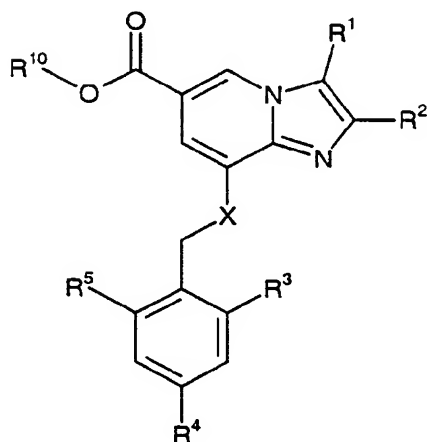


III

wherein R^6 and R^7 are as defined in claim 1, under standard conditions, to a compound of Formula I wherein R^1 is H or CH_3 and X is NH.

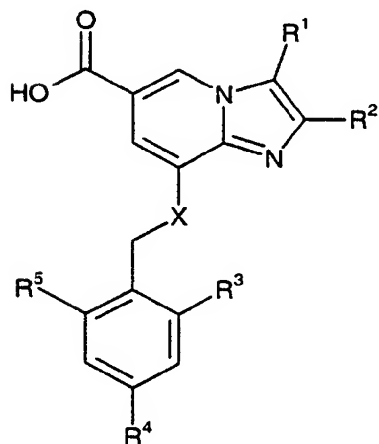
10. A process for the preparation of a compound according to any one of claims 1 to 5 comprising

(a) treating a compound of Formula XVII



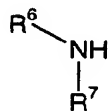
XVII

wherein R^1 , R^2 , R^3 , R^4 , R^5 and X are as defined in claim 1 and R^{10} is an alkyl group, with acid or base under standard conditions to a compound of Formula XVIII



XVIII

(b) reacting a compound of Formula XVIII wherein R¹, R², R³, R⁴, R⁵ and X is defined in claim 1 with a compound of Formula III

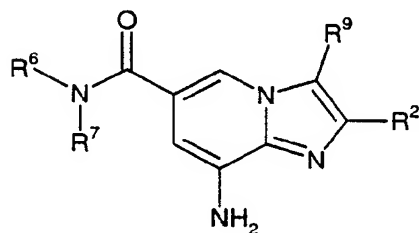


III

wherein R⁶ and R⁷ are as defined in claim 1, in the presence of a coupling reagent in an inert solvent under standard conditions, to a compound of Formula I.

11. A compound according to any one of claims 1 to 5 for use in therapy.
12. A pharmaceutical formulation containing a compound according to any one of claims 1 to 5 as active ingredient in combination with a pharmaceutically acceptable diluent or carrier.
13. Use of a compound according to any one of claims 1 to 5 for the manufacture of a medicament for the inhibition of gastric acid secretion.
14. Use of a compound according to any one of claims 1 to 5 for the manufacture of a medicament for the treatment of gastrointestinal inflammatory diseases.
15. Use of a compound according to any one of claims 1 to 5 the manufacture of a medicament for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, wherein the said salt is adapted to be administered in combination with at least one antimicrobial agent.
16. A method for inhibiting gastric acid secretion which comprises administering to a mammal, including man, in need of such inhibition an effective amount of a compound according to any one of claims 1 to 5.

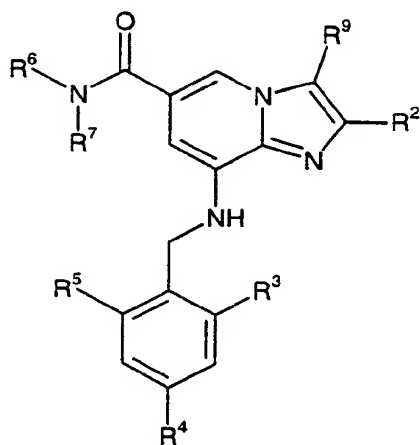
17. A method for the treatment of gastrointestinal inflammatory diseases which comprises administering to a mammal, including man, in need of such treatment an effective amount of a compound according to any one of claims 1 to 5.
- 5 18. A method for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, which comprises administering to a mammal, including humans, in need of such treatment an effective amount of a compound as claimed in any one of claims 1 to 5, wherein the said salt is administered in combination with at least one antimicrobial agent.
- 10 19. A pharmaceutical formulation for use in the inhibition of gastric acid secretion wherein the active ingredient is a compound according to any one of claims 1 to 5.
- 15 20. A pharmaceutical formulation for use in the treatment of gastrointestinal inflammatory diseases wherein the active ingredient is a compound according to any one of claims 1 to 5.
- 20 21. A pharmaceutical formulation for use in the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, wherein the active ingredient is a compound according to any one of claims 1 to 5 in combination for simultaneous, separate or sequential use or together with at least one antimicrobial agent.
- 25 22. A compound of the formula VIII



VIII

wherein R^2 , R^6 and R^7 are as defined in claim 1, and R^9 is H, CH_3 or an ester group.

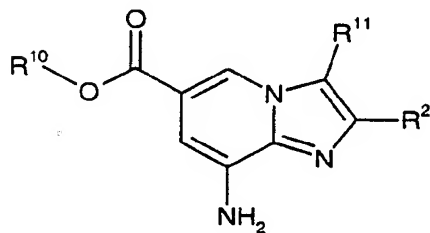
23. A compound of the formula X



X

wherein R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined in claim 1, and R^9 is an ester group.

24. A compound of the formula XV

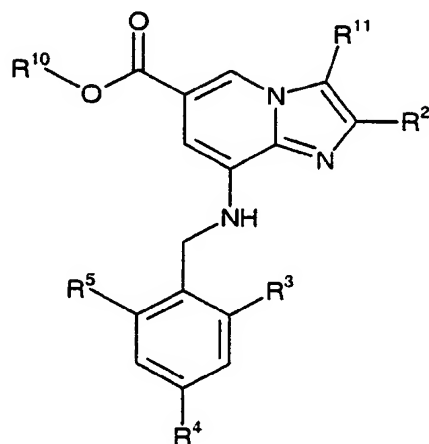


XV

wherein R^2 is as defined in claim 1, R^{10} is an alkyl group and R^{11} is H or CH_3 .

70

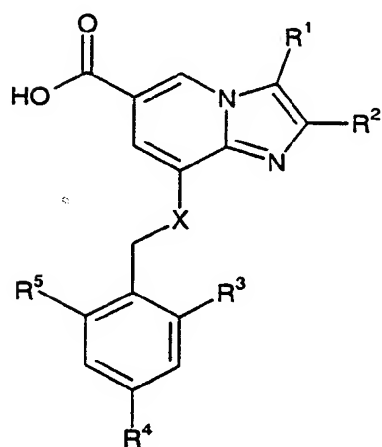
25. A compound of the formula XVI



XVI

5 wherein R², R³, R⁴ and R⁵ are as defined in claim 1, R¹⁰ is an alkyl group and R¹¹ is H or CH₃.

26. A compound of the formula



10

XVIII

wherein R¹, R², R³, R⁴ R⁵ and X are as defined in claim 1.

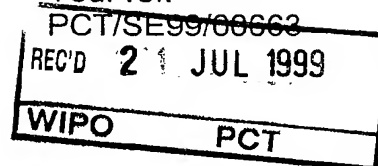
Patent- och Registreringsverket
Box 5055
102 42 STOCKHOLM

Första Posten

June 8, 1999

Our ref.
H 1982-1 WO

Your ref.



Re: Request to correct obvious errors according to PCT-rule 91.

Dear Sirs,

We hereby kindly request rectification of the specification of the above identified international patent application in accordance with PCT-rule 91.1(d). The request refers to correction of obvious typing errors.

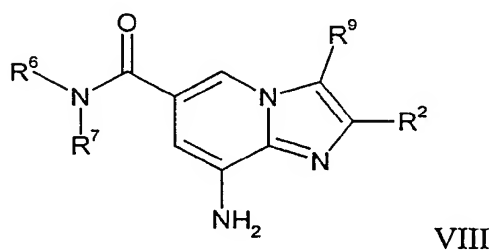
Please find enclosed substitute sheets, page 9, 12-14, 19-20, 62, 65-66, 69-70, wherein the substituents denoted R^4 and R^5 have been replaced, whereby each and every formula have regained its original substitution pattern found e.g. in the general Formula I on page 2 and in all other related formulas.

We earnestly request that the substitute sheets are included in the present application before publishing.

Yours sincerely,

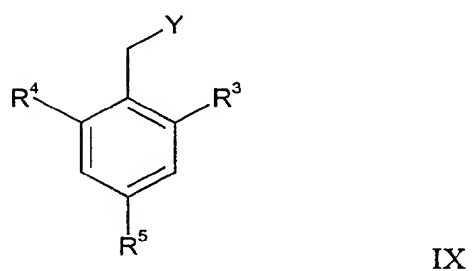
Christer Hällgren, Ph.D.
Astra AB

The reaction is carried out under standard conditions in an inert solvent such as acetone, acetonitrile, alcohol, dimethylformamide, etc. with or without a base.

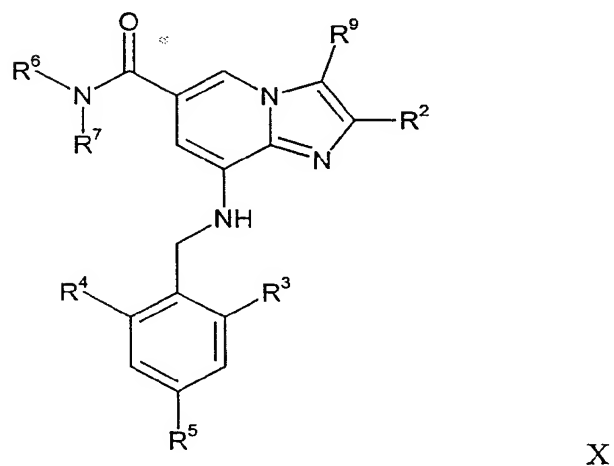


5

e) Compounds of the Formula VIII can be reacted with compounds of the Formula IX

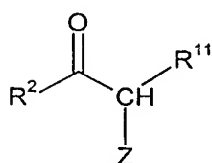


10 wherein R³, R⁴ and R⁵ are as defined for Formula I and Y is a leaving group, such as a halide, tosyl or mesyl, to the compounds of the Formula X.



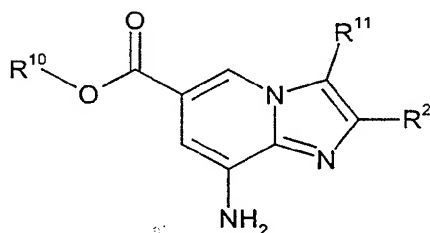
wherein R^{10} is an alkyl group such as methyl, ethyl etc. The reaction can be carried out under standard conditions in an inert solvent.

d) The imidazo[1,2-a]pyridine compounds of the Formula XV wherein R^{10} is an alkyl group such as methyl, ethyl etc, can be prepared by reacting compounds of the general Formula XIII with compounds of the general Formula XIV



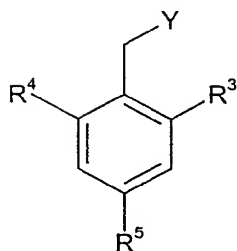
XIV

wherein R^2 is as defined for Formula I, Z is a leaving group such as halogen, mesyl or tosyl and R^{11} represents H or CH_3 . The reaction is carried out under standard conditions in an inert solvent such as acetone, acetonitrile, alcohol, dimethylformamide etc, with or without a base.



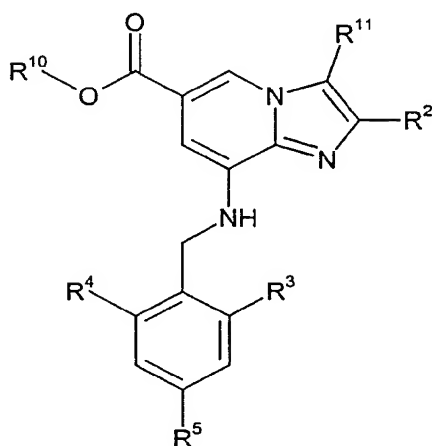
XV

e) Compounds of the Formula XV can be reacted with compounds of the Formula IX



IX

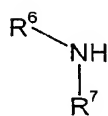
wherein R^3 , R^4 and R^5 are as defined for Formula I and Y is a leaving group, such as a halide, tosyl or mesyl, to the compounds of the Formula XVI.



XVI

wherein R^2 , R^3 , R^4 and R^5 are as defined for Formula I, R^{10} is an alkyl group such as methyl, ethyl, etc. and R^{11} is H, or CH_3 . It is convenient to conduct this reaction in an inert solvent, e.g. acetone, acetonitrile, dimethoxyethane, methanol, ethanol or dimethylformamide with or without a base. The base is e.g. an alkali metal hydroxide, such as sodium hydroxide and potassium hydroxide, an alkali metal carbonate, such as potassium carbonate and sodium carbonate; or an organic amine, such as triethylamine.

f) Compounds of the Formula XVI can be reacted with amino compounds of the general Formula III



III

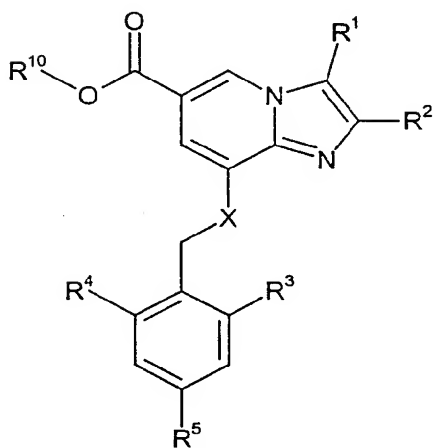
wherein R^6 and R^7 are as defined in Formula I to the corresponding amide of the Formula I wherein R^1 is H or CH_3 and X is NH. The reaction can be carried out by heating the reactants in the neat amino compound or in an inert solvent under standard conditions.

Process C

Process C for manufacture of compounds with the general Formula I comprises the following steps:

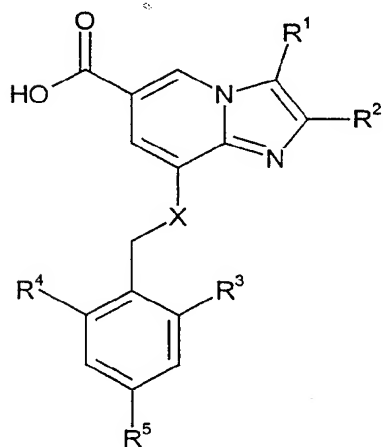
5

a) Treating compounds of Formula XVII



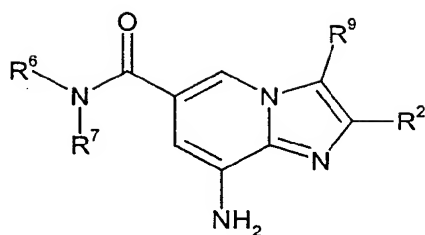
XVII

10 wherein R¹, R², R³, R⁴, R⁵, and X are as defined in Formula I and R¹⁰ is an alkyl group such as methyl, ethyl, etc, with acid or base under standard conditions can hydrolyzed them to the corresponding carboxylic acid compounds of Formula XVIII



XVIII

15

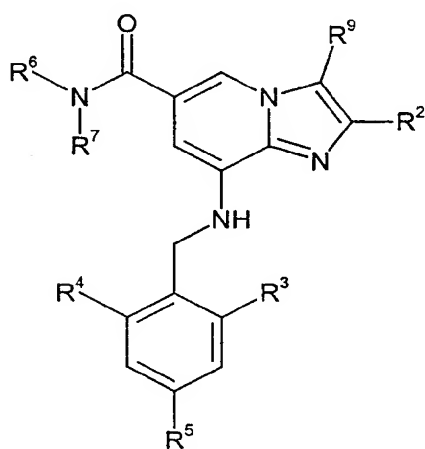


VIII

wherein R^2 , R^6 and R^7 are as defined for Formula I, and R^9 is H, CH^3 or an ester group such as $COOCH_3$, $COOC_2H_5$, etc.;

5

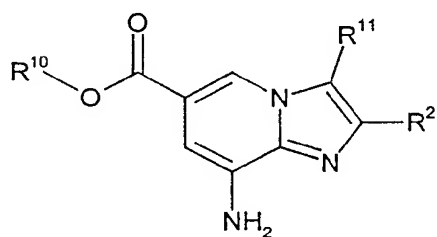
(b) a compound of the formula X



X

10 wherein R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined for Formula I, and R^9 is an ester group such as $COOCH_3$, $COOC_2H_5$ etc.;

(c) a compound of the formula XV

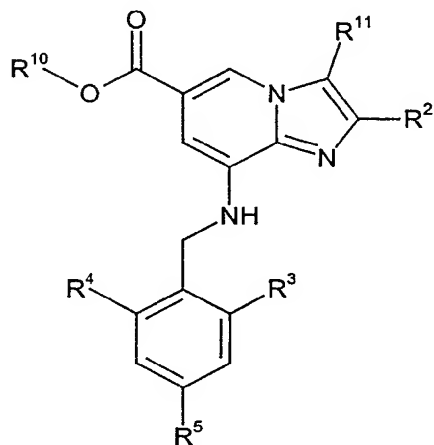


XV

15

wherein R^2 is as defined for Formula I, R^{10} is an alkyl group and R^{11} is H or CH_3 ;

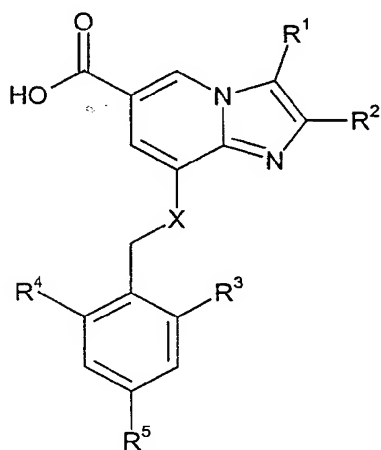
(d) a compound of the formula XVI



XVI

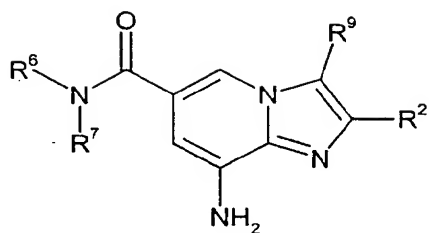
wherein R^2 , R^3 , R^4 and R^5 are as defined for Formula I, R^{10} is an alkyl group and R^{11} is H or CH_3 ;

10 (e) a compound of the formula XVIII



XVIII

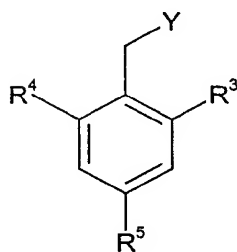
wherein R^1 , R^2 , R^3 , R^4 , R^5 and X are as defined for



VIII

(e) reacting a compound of the Formula VIII wherein R^6 , R^7 and R^2 are as defined in claim 1, and R^9 is H, CH_3 or an ester group with a compound of Formula IX

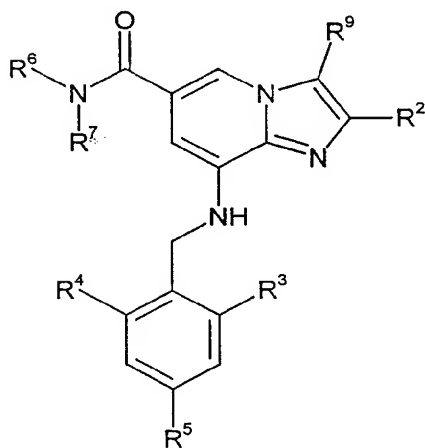
5



IX

wherein R^3 , R^4 , and R^5 are as defined in claim 1, and Y is a leaving group in an inert solvent with or without a base, to a compound of the Formula X

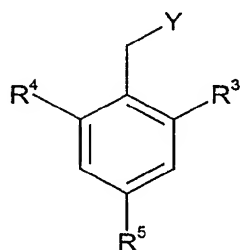
10



X

(f) reducing a compound of Formula X wherein R^9 is an ester group in an inert solvent to a compound of the Formula I wherein R^1 is CH_2OH and X is NH.

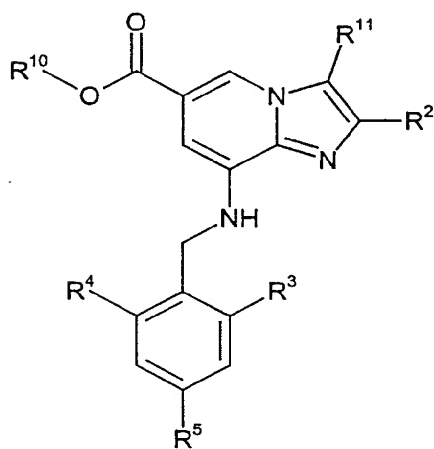
(e) reacting a compound of the Formula XV wherein R^{10} is an alkyl group, R^2 are as defined in claim 1 and R^{11} is H or CH_3 with a compound of Formula IX



IX

5

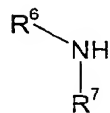
wherein R^3 , R^4 , and R^5 are as defined in claim 1 and Y is a leaving group in an inert solvent with or without a base to a compound of the Formula XVI



XVI

10

(f) reacting a compound of Formula XVI wherein R^2 , R^3 , R^4 and R^5 are as defined in claim 1, R^{10} is an alkyl group and R^{11} is H or CH_3 with a compound of Formula III



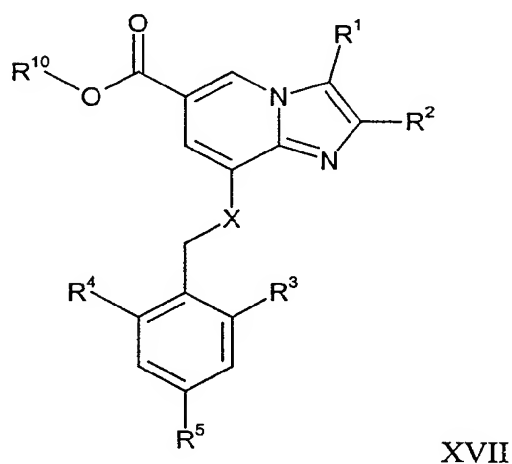
III

15

wherein R^6 and R^7 are as defined in claim 1, under standard conditions, to a compound of Formula I wherein R^1 is H or CH_3 and X is NH.

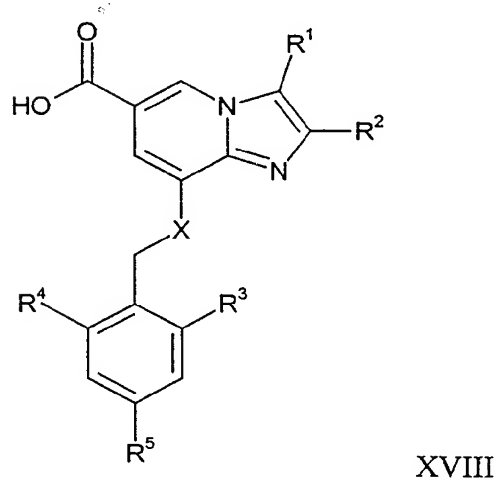
10. A process for the preparation of a compound according to any one of claims 1 to 5 comprising

(a) treating a compound of Formula XVII



XVII

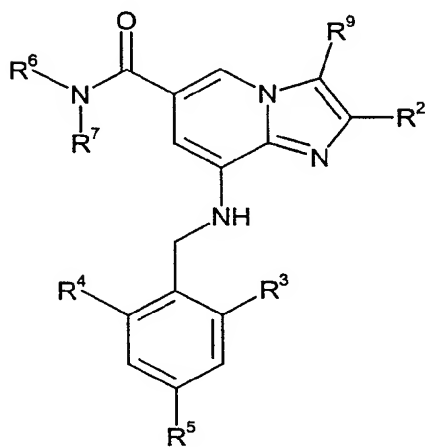
wherein R^1 , R^2 , R^3 , R^4 , R^5 and X are as defined in claim 1 and R^{10} is an alkyl group, with acid or base under standard conditions to a compound of Formula XVIII



XVIII

wherein R^2 , R^6 and R^7 are as defined in claim 1, and R^9 is H, CH_3 or an ester group.

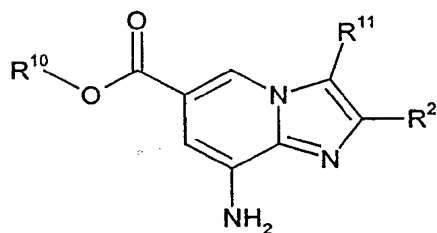
23. A compound of the formula X



X

wherein R^2 , R^3 , R^4 , R^5 , R^6 and R^7 are as defined in claim 1, and R^9 is an ester group.

24. A compound of the formula XV



XV

wherein R^2 is as defined in claim 1, R^{10} is an alkyl group and R^{11} is H or CH_3 .

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00663

A. CLASSIFICATION OF SUBJECT MATTER		
IPC6: C07D 471/04, A61K 31/435 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC6: C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0308917 A2 (FUJISAWA PHARMACEUTICAL, CO., LTD.), 29 March 1989 (29.03.89) --	1-15,19-23
A	J. Med. Chem., Volume 28, 1985, James J. Kaminski et al, "Antiulcer Agents. 1. Gastric Antisecretory and Cytoprotective Properties of Substituted Imidazo(1,2-a)pyridines" page 876 - page 892 --	1-15,19-23
A	EP 0033094 A1 (SCHERING CORPORATION), 5 August 1981 (05.08.81) --	1-15,19-23
A	EP 0228006 A1 (FUJISAWA PHARMACEUTICAL CO., LTD.), 8 July 1987 (08.07.87) --	1-15,19-23
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
9 Sept 1999		10-09-1999
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86		Authorized officer Göran Karlsson/Els Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 99/00663

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0204285 A1 (FUJISAWA PHARMACEUTICAL CO., LTD.), 10 December 1986 (10.12.86) -- -----	1-15,19-23

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00663

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16-18
because they relate to subject matter not required to be searched by this Authority, namely:
**A method for treatment of the human or animal body by therapy,
see rule 39.1**
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such
an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-15, 19-23**

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00663

The subjects, defined by the problems and their means of solution, as listed below are so different from each other that no technical relationship or interaction can be appreciated to be present so as to form a single general inventive concept. The acceptance of a single general inventive concept covering the end products as well as products used to prepare these and products (intermediates) implies that when several claimed intermediates are implied in different reactions, these intermediates are technically closely inter-connected with the end products as well as with themselves by their use for incorporation of the same essential structural part into the end products.

1. claims 1-15, 19-21 and claims 22 and 23, intermediates VIII and X
2. claim 24, intermediate XV
3. claims 25 and 26, intermediates XVI and XVIII

The special technical feature of invention 1 is compound I containing an amide group in position 6 and intermediates VIII and X, which are specially designed for the preparation of compound I. Compounds I, VIII and X do not contain a common technical feature together with intermediates XV, XVI or XVIII. Therefore, a single inventive concept based on the relationship intermediates/end products is lacking.

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/08/99

International application No.

PCT/SE 99/00663

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
EP	0308917	A2	29/03/89	AU	2278388 A	06/04/89
				CN	1033628 A	05/07/89
				DK	532088 A	25/03/89
				FI	884318 A	25/03/89
				JP	1151579 A	14/06/89
				US	4920129 A	24/04/90
EP	0033094	A1	05/08/81	SE	0033094 T3	
				AU	540840 B	06/12/84
				AU	6633781 A	30/07/81
				CA	1167845 A	22/05/84
				DK	25081 A	24/07/81
				FI	810147 A	24/07/81
				GR	72960 A	19/01/84
				HK	94187 A	18/12/87
				IE	50682 B	11/06/86
				JP	56113782 A	07/09/81
				MY	76087 A	31/12/87
				NZ	196071 A	31/05/84
				OA	6727 A	30/06/82
				PT	72370 A,B	01/02/81
				ZA	8100219 A	27/01/82
EP	0228006	A1	08/07/87	AT	71625 T	15/02/92
				AU	593802 B	22/02/90
				AU	5834586 A	11/12/86
				CA	1257264 A	11/07/89
				DE	3683403 A	27/02/92
				DK	250386 A	05/12/86
				EP	0204285 A,B	10/12/86
				FI	862210 A	05/12/86
				GR	861379 A	28/08/86
				JP	62187471 A	15/08/87
				US	4725601 A	16/02/88
				US	4782055 A	01/11/88
EP	0204285	A1	10/12/86	AT	71625 T	15/02/92
				AU	593802 B	22/02/90
				AU	5834586 A	11/12/86
				CA	1257264 A	11/07/89
				DE	3683403 A	27/02/92
				DK	250386 A	05/12/86
				FI	862210 A	05/12/86
				GR	861379 A	28/08/86
				JP	62016483 A	24/01/87
				US	4725601 A	16/02/88
				EP	0228006 A	08/07/87
				JP	62187471 A	15/08/87
				US	4782055 A	01/11/88



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 471/04, A61K 31/435	A2	(11) International Publication Number: WO 00/10999 (43) International Publication Date: 2 March 2000 (02.03.00)		
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> (21) International Application Number: PCT/SE99/01401 (22) International Filing Date: 18 August 1999 (18.08.99) (30) Priority Data: 9802793-1 21 August 1998 (21.08.98) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): AMIN, Kosrat [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). DAHLSTRÖM, Mikael [FI/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). NORDBERG, Peter [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). STARKE, Ingemar [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE). </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i> </td> </tr> </table>			(21) International Application Number: PCT/SE99/01401 (22) International Filing Date: 18 August 1999 (18.08.99) (30) Priority Data: 9802793-1 21 August 1998 (21.08.98) SE (71) Applicant (for all designated States except US): ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE). (72) Inventors; and (75) Inventors/Applicants (for US only): AMIN, Kosrat [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). DAHLSTRÖM, Mikael [FI/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). NORDBERG, Peter [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). STARKE, Ingemar [SE/SE]; Astra Hässle AB, S-431 83 Mölndal (SE). (74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).	(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
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(54) Title: NEW COMPOUNDS				
<div style="position: absolute; left: 660px; top: 620px;">(I)</div>				
(57) Abstract <p>The present invention relates to novel compounds, and therapeutically acceptable salts thereof of formula (I), which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases.</p>				

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NEW COMPOUNDS

TECHNICAL FIELD

5 The present invention relates to novel compounds, and therapeutically acceptable salts thereof, which inhibit exogenously or endogenously stimulated gastric acid secretion and thus can be used in the prevention and treatment of gastrointestinal inflammatory diseases. In further aspects, the invention relates to compounds of the invention for use in therapy; to processes for preparation of such new compounds; to pharmaceutical compositions
10 containing at least one compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient; and to the use of the active compounds in the manufacture of medicaments for the medical use indicated above.

15 BACKGROUND ART

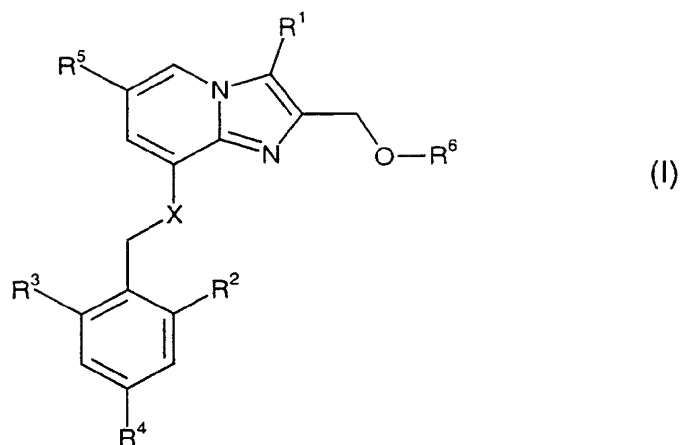
Substituted imidazo[1,2-a]pyridines, useful in the treatment of peptic ulcer diseases, are known in the art, e.g. from EP-B-0033094 and US 4,450,164 (Schering Corporation); from EP-B-0204285 and US 4,725,601 (Fujisawa Pharmaceutical Co.); and from publications by
20 J. J. Kaminski et al. in the Journal of Medical Chemistry (vol. 28, 876-892, 1985; vol. 30, 2031-2046, 1987; vol. 30, 2047-2051, 1987; vol. 32, 1686-1700, 1989; and vol. 34, 533-541, 1991).

For a review of the pharmacology of the gastric acid pump (the H⁺, K⁺-ATPase), see Sachs
25 et al. (1995) Annu. Rev. Pharmacol. Toxicol. 35: 277-305.

DISCLOSURE OF THE INVENTION

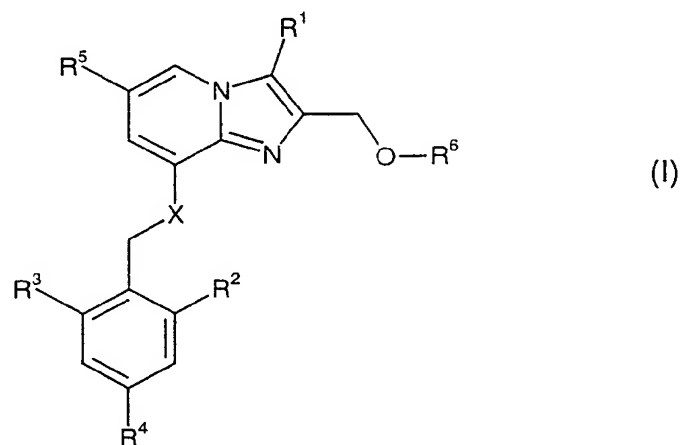
It has surprisingly been found that compounds of the Formula I

2



or a pharmaceutically acceptable salt thereof, are particularly effective as inhibitors of the gastrointestinal H⁺, K⁺-ATPase and thereby as inhibitors of gastric acid secretion.

In one aspect, the invention thus relates to compounds of the general Formula I



or a pharmaceutically acceptable salt thereof, wherein

R¹ is

- (a) H,
- (b) CH₃, or
- (c) CH₂OH;

R² is C₁-C₆ alkyl;

R^3 is C_1 - C_6 alkyl;

R^4 is

- (a) H, or
(b) halogen;

R^5 is

- (a) H, or
(b) C_1 - C_6 alkyl;

R^6 is

- (a) H,
(b) C_1 - C_6 alkyl carbonyl

(c) C_3 - C_7 cycloalkyl carbonyl, in which the cycloalkyl group is optionally substituted by one or more substituents selected from, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -COOH or -COO-(C_1 - C_6) alkyl

(d) Aryl C_1 - C_6 alkyl carbonyl, in which aryl represents phenyl, pyridyl, thienyl or furanyl, optionally substituted by one or more substituents selected from, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -COOH or -COO-(C_1 - C_6) alkyl

(e) C_1 - C_6 alkoxy C_1 - C_6 alkyl carbonyl

(f) C_1 - C_6 alkoxy carbonyl

(g) aryl carbonyl, in which aryl represents phenyl, pyridyl, thienyl or furanyl, optionally

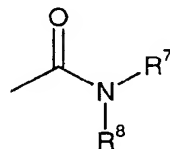
substituted by one or more substituents selected from, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -COOH or -COO-(C_1 - C_6) alkyl

(h) C_3 - C_7 cycloalkyl C_1 - C_6 alkylcarbonyl, in which the cycloalkyl group is optionally substituted by one or more substituents selected from, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, -COOH or -COO-(C_1 - C_6) alkyl

(i) C₁-C₆ alkoxy C₁-C₆ alkoxy carbonyl

(j) C₁-C₆ alkoxy C₁-C₆ alkoxy C₁-C₆ alkyl carbonyl

5 (k) a carbamoyl group with the formula



wherein R⁷, R⁸ are the same or different and are H, or C₁-C₆ alkyl

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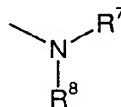
(l) R⁹-(C₁-C₆) alkyl carbonyl

wherein R⁹ is

15

HOC=O-, C₁-C₆ alkyl-O-C=O-, or

an aminogroup with the formula



20

wherein R⁷, R⁸ are the same or different and are H, or C₁-C₆ alkyl

(m) R⁹-hydroxylated-(C₁-C₆) alkyl carbonyl

(n) R⁹-(C₁-C₆) alkenyl carbonyl

25

X is

(a) NH, or

(b) O.

30

As used herein, the term "C₁-C₆ alkyl" denotes a straight or branched alkyl group having from 1 to 6 carbon atoms. Examples of said C₁-C₆ alkyl include methyl, ethyl, n-propyl,

iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl and straight- and branched-chain pentyl and hexyl.

The term "halogen" includes fluoro, chloro, bromo and iodo.

5

The term "pyridyl" includes the 2-, 3-, and 4-isomers and the terms thienyl and furanyl include the 2-, and 3-isomers.

10

Both the pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers are within the scope of the invention. It should be understood that all the diastereomeric forms possible (pure enantiomers, racemic mixtures and unequal mixtures of two enantiomers) are within the scope of the invention. Also included in the invention are derivatives of the compounds of the Formula I which have the biological function of the compounds of the Formula I.

15

Depending on the process conditions the end products of the Formula I are obtained either in neutral or salt form. Both the free base and the salts of these end products are within the scope of the invention.

20

Acid addition salts of the new compounds may in a manner known *per se* be transformed into the free base using basic agents such as alkali or by ion exchange. The free base obtained may also form salts with organic or inorganic acids.

25

In the preparation of acid addition salts, preferably such acids are used which form suitably therapeutically acceptable salts. Examples of such acids are hydrohalogen acids such as hydrochloric acid, sulphuric acid, phosphoric acid, nitric acid, aliphatic, alicyclic, aromatic or heterocyclic carboxyl or sulphonc acids, such as formic acid, acetic acid, propionic acid, succinic acid, glycolic acid, lactic acid, malic acid, tartaric acid, citric acid, ascorbic acid, maleic acid, hydroxymaleic acid, pyruvic acid, p-hydroxybenzoic acid, embonic acid, methanesulphonic acid, ethanesulphonic acid, hydroxyethanesulphonic acid, halogenbenzenesulphonic acid, toluenesulphonic acid or naphthalenesulphonic acid.

30

Preferred compounds according to the invention are those of Formula I wherein R^1 is CH_3 or CH_2OH ; R^2 is CH_3 or CH_2CH_3 ; R^3 is CH_3 or CH_2CH_3 ; R^4 is H, Br, Cl or F; R^5 is H or CH_3 .

5

Particularly preferred compounds according to the invention are:

8-(2,6-dimethylbenzylamino)-2-hydroxymethyl-3-methylimidazo[1,2-a]pyridine

10 8-(2-ethyl-6-methylbenzylamino)-2-hydroxymethyl-3-methylimidazo[1,2-a]pyridine

8-(2,6-dimethylbenzylamino)-3,6-dimethyl-2-hydroxymethylimidazo[1,2-a]pyridine

15 [8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methyl acetate

[8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methyl ethyl carbonate

[8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methyl N,N-dimethylcarbamate

20

-1-[[8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methyl] 3-ethyl malonate .

25 4-[[8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methoxy]-4-oxobutanoic acid

4-[[8-(2-ethyl-6-methylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methoxy]-4-oxobutanoic acid

30 5-[[8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methoxy]-5-oxopentanoic acid

[8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methyl 2-(dimethylamino)acetate

5 8-(2,6-dimethylbenzylamino)-2,3-dihydroxymethyl-imidazo[1,2-a]pyridine

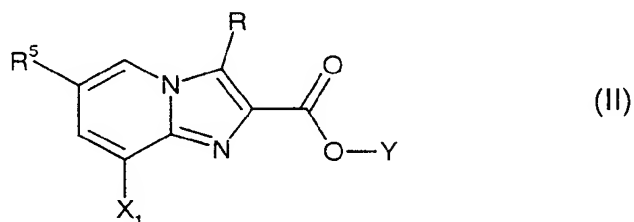
Preparation

10 The present invention also provides the following processes A and B for the manufacture of compounds with the general Formula I.

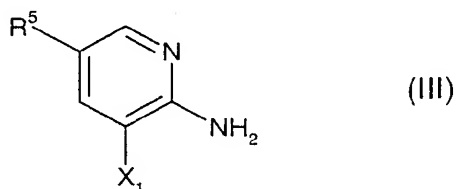
The process A for manufacture of compounds with the general Formula I comprises the following steps:

15

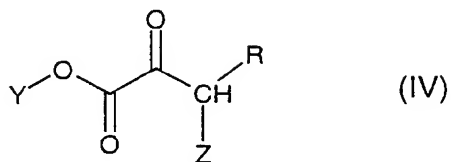
a) The imidazo[1,2-a]pyridine compounds of the Formula II



20 wherein Y is a lower alkyl group, R represents H, CH₃ or an ester group such as COOCH₃, COOC₂H₅ etc, X₁ is NH₂ or OH and R⁵ is as defined for Formula I, can be prepared by reacting compounds of the general Formula III



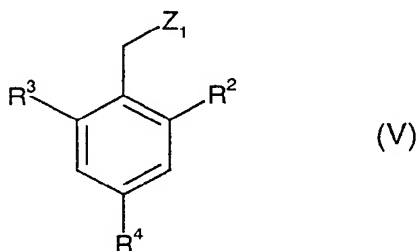
with compounds of the general Formula IV



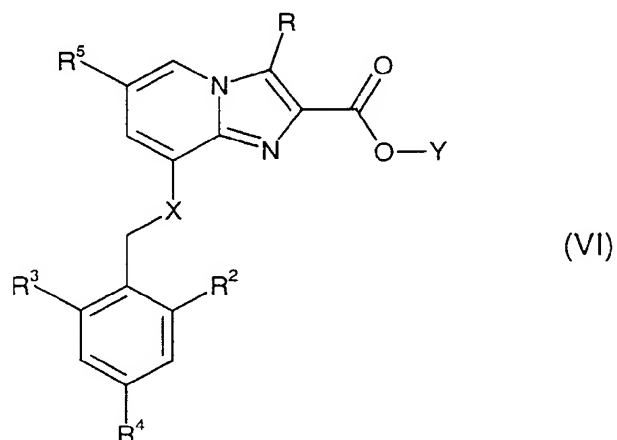
wherein Z is a leaving group such as halogen, mesyl, or tosyl.

The reaction is carried out under standard conditions in an inert solvent such as acetone, acetonitrile, alcohol, N,N-dimethylformamide e.t.c with or without a base.

b) Compounds of the Formula II can be reacted with compounds of the Formula V



wherein R^2 , R^3 and R^4 are as defined for Formula I and Z_1 is a leaving group, such as halogen, tosyl or mesyl, under standard conditions in an inert solvent, with or without a base, to compounds of Formula VI



wherein R^2 , R^3 , R^4 , R^5 and X are as defined for Formula I, Y is a lower alkyl group and R is H, CH_3 or an ester group such as $COOCH_3$, $COOC_2H_5$ e.t.c.

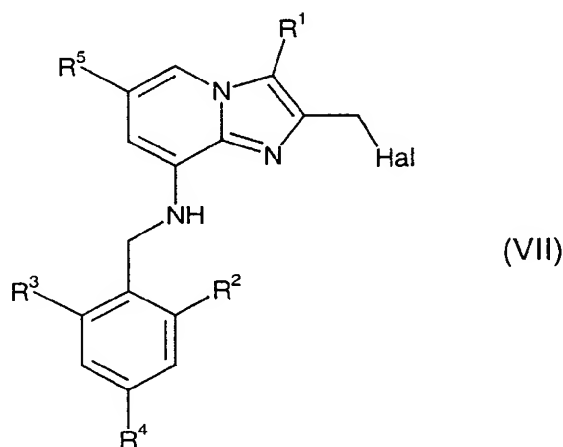
- 5 c) Reduction of compounds of the general Formula VI e.g. by using lithium aluminium hydride or Red-Al in an inert solvent such as tetrahydrofuran, ether or toluene yields the compounds of the general Formula I wherein R^6 is H.

- 10 d) The substituent R^6 of Formula I ($R^6 \neq H$) can be introduced by standard acylating procedures carried out under standard conditions, eg. by reacting compounds of Formula I, wherein R^6 is H, with the acid, acid halide or the anhydride of R^6 ($R^6 \neq H$).

The process B for manufacture of compounds with the general Formula I comprises the following steps:

15

- a) In compounds of Formula I wherein R^6 is H, the hydroxymethyl group can be halogenated by standard methods in an inert solvent, to the corresponding halogenmethyl group of Formula VII



20

- b) The substituent R^6 of Formula I ($R^6 \neq H$) can be introduced by reacting compounds of Formula VII with the corresponding acid of R^6 ($R^6 \neq H$). The reaction is carried out under standard conditions in an inert solvent with or without a base.

25

Medical use

In a further aspect, the invention relates to compounds of the formula I for use in therapy, in particular for use against gastrointestinal inflammatory diseases. The invention also
5 provides the use of a compound of the formula I in the manufacture of a medicament for the inhibition of gastric acid secretion, or for the treatment of gastrointestinal inflammatory diseases.

The compounds according to the invention may thus be used for prevention and treatment
10 of gastrointestinal inflammatory diseases, and gastric acid-related diseases in mammals including man, such as gastritis, gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable, e.g. in patients with gastrinomas, and in patients with acute upper gastrointestinal bleeding. They
15 may also be used in patients in intensive care situations, and pre-and postoperatively to prevent acid aspiration and stress ulceration.

The typical daily dose of the active substance varies within a wide range and will depend on various factors such as for example the individual requirement of each patient, the route
20 of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 1000 mg per day of active substance.

Pharmaceutical formulations

25 In yet a further aspect, the invention relates to pharmaceutical compositions containing at least one compound of the invention, or a therapeutically acceptable salt thereof, as active ingredient.

The compounds of the invention can also be used in formulations together with other active
30 ingredients, e.g. antibiotics such as amoxicillin.

For clinical use, the compounds of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other mode of administration. The pharmaceutical formulation contains a compound of the invention in combination with one or more pharmaceutically acceptable ingredients. The carrier may be in the form of a solid, semi-solid or liquid diluent, or a capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compounds is between 0.1–95% by weight of the preparation, preferably between 0.1–20% by weight in preparations for parenteral use and preferably between 0.1 and 50% by weight in preparations for oral administration.

In the preparation of pharmaceutical formulations containing a compound of the present invention in the form of dosage units for oral administration the compound selected may be mixed with solid, powdered ingredients, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable ingredient, as well as with disintegrating agents and lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylene glycol waxes. The mixture is then processed into granules or pressed into tablets.

Soft gelatin capsules may be prepared with capsules containing a mixture of the active compound or compounds of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatin capsules. Hard gelatin capsules may contain granules of the active compound. Hard gelatin capsules may also contain the active compound in combination with solid powdered ingredients such as lactose, saccharose, sorbitol, mannitol, potato starch, corn starch, amylopectin, cellulose derivatives or gelatin.

Dosage units for rectal administration may be prepared (i) in the form of suppositories which contain the active substance mixed with a neutral fat base; (ii) in the form of a gelatin rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatin rectal capsules; (iii) in the form of a ready-made micro enema; or (iv) in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.1% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and polyethylene glycol. If desired, such liquid preparations may contain coloring agents, flavoring agents, saccharine and carboxymethyl cellulose or other thickening agent. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

Solutions for parenteral administration may be prepared as a solution of a compound of the invention in a pharmaceutically acceptable solvent, preferably in a concentration from 0.1% to 10% by weight. These solutions may also contain stabilizing ingredients and/or buffering ingredients and are dispensed into unit doses in the form of ampoules or vials. Solutions for parenteral administration may also be prepared as a dry preparation to be reconstituted with a suitable solvent extemporaneously before use.

The compounds according to the invention can also be used in formulations together with other active ingredients, e.g. for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa. Such other active ingredients may be antimicrobial agents, in particular:

- β -lactam antibiotics such as amoxicillin, ampicillin, cephalothin, cefaclor or cefixime;
- macrolides such as erythromycin, or clarithromycin;
- tetracyclines such as tetracycline or doxycycline;
- aminoglycosides such as gentamycin, kanamycin or amikacin;
- quinolones such as norfloxacin, ciprofloxacin or enoxacin;
- others such as metronidazole, nitrofurantoin or chloramphenicol; or
- preparations containing bismuth salts such as bismuth subcitrate, bismuth subsalicylate, bismuth subcarbonate, bismuth subnitrate or bismuth subgallate.

The compounds according to the present invention can also be used together or in combination for simultaneous, separate or sequential use with antacids such as aluminium hydroxide, magnesium carbonate and magnesium hydroxid or alginic acid, or together or in combination for simultaneous, separate or sequential use with
5 pharmaceuticals which inhibit acid secretion, such as, H₂-blockers (*e.g.* cimetidine, ranitidine), H⁺/K⁺ - ATPase inhibitors (*e.g.* omeprazole, pantoprazole, lansoprazole or rabeprazole), or together or in combination for simultaneous, separate or sequential use with gastroprokinetics (*e.g.* cisapride or mosapride).

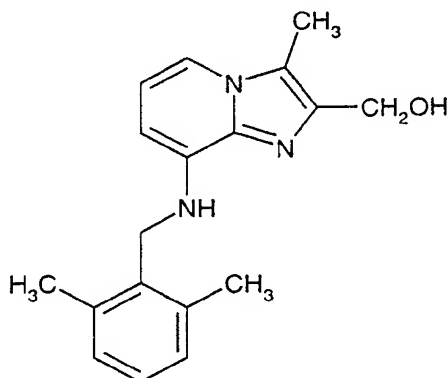
10 *Examples*

1. PREPARATION OF COMPOUNDS OF THE INVENTION

Example 1.1

15

Synthesis of 8-(2,6-dimethylbenzylamino)-2-hydroxymethyl-3-methylimidazo[1,2-a]pyridine



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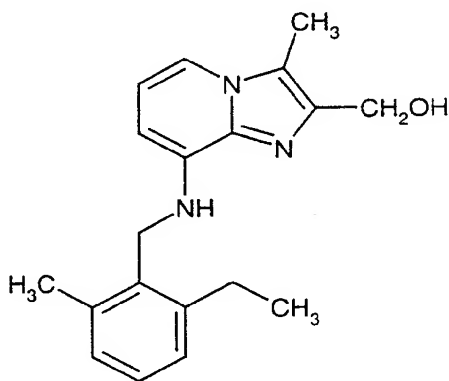
Ethyl 8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-carboxylate (5.2 g, 0.015 mol) was solved in tetrahydrofuran (100 ml) and LiAlH₄ (1.15 g 0.03 mol) was added. After stirring the mixture at room temperature. for 45 min, 1.15 ml of water was
25 added dropwise, followed by 1.15 ml of 15% sodium hydroxide and then 3.45 ml of water. The solids were removed by filtration and washed thoroughly with methylene chloride. The filtrate and washings were combined and dried and the solvents were removed under

reduced pressure. Purification of the residue by column chromatography on silica gel using methylene chloride : methanol (10:2) as eluent gave 3.2 g (73%) of the title compound.

¹H-NMR (300 MHz, DMSO-d₆): δ 2.35 (s, 6H), 2.4 (s, 3H), 4.35 (d, 2H), 4.5 (d, 2H), 4.85 (t, 1H), 4.9 (t, 1H), 6.3 (s, 1H), 6.8 (t, 1H), 7.05-7.2 (m, 3H), 7.55 (d, 1H)

Example 1.2

Synthesis of 8-(2-ethyl-6-methylbenzylamino)-2-hydroxymethyl-3-methylimidazo[1,2-a]pyridine

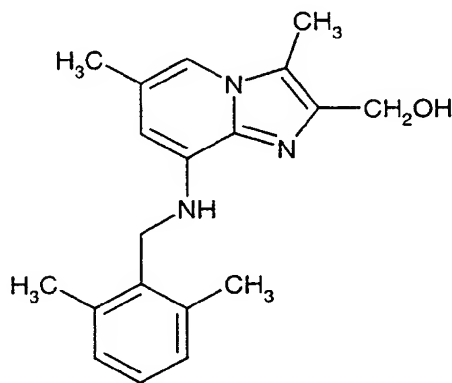


To a suspension of LiAlH₄ (0.24 g, 6.4 mmol) in anhydrous tetrahydrofuran (25 ml) in an argon atmosphere was added dropwise during 30 min. ethyl 8-(2-ethyl-6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-carboxylate (1.1 g, 3.2 mmol) dissolved in anhydrous tetrahydrofuran (25 ml). After stirring the mixture at room temperature for 4 h, 0.24 ml of water was added dropwise, followed by 0.24 ml of 15% sodium hydroxide and then 0.75 ml of water. The solids were removed by filtration and washed thoroughly with tetrahydrofuran and methylene chloride: methanol (9:1). The filtrate and washings were combined and dried and the solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel using methylene chloride: methanol (9:1) as eluent. Treating the residue with acetonitrile and filtration gave 0.76 g (77%) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 1.2 (t, 3H), 2.3 (s, 3H), 2.4 (s, 3H), 2.75 (q, 2H), 4.35 (d, 2H), 4.45 (s, 2H), 4.75 (bs, 1H), 5.45 (t, 1H), 6.2 (d, 1H), 6.75 (t, 1H), 7.05-7.25 (m, 4H)

Example 1.3

Synthesis of 8-(2,6-dimethylbenzylamino)-3,6-dimethyl-2-hydroxymethylimidazo[1,2-a]pyridine



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To a suspension of LiAlH_4 (0.19 g, 5.1 mmol) in anhydrous tetrahydrofuran (15 ml) in an argon atmosphere was added dropwise during 30 min ethyl 8-(2-ethyl-6-dimethylbenzylamino)-3,6-dimethylimidazo[1,2-a]pyridin-2-carboxylate (0.9 g, 2.6 mmol) solved in anhydrous tetrahydrofuran (15 ml). After stirring the mixture at room temperature for 2 h, 0.2 ml of water was added dropwise, followed by 0.2 ml of 15% sodium hydroxide and then 0.6 ml of water. The solids were removed by filtration and washed thoroughly with methylene chloride: methanol (1:1)

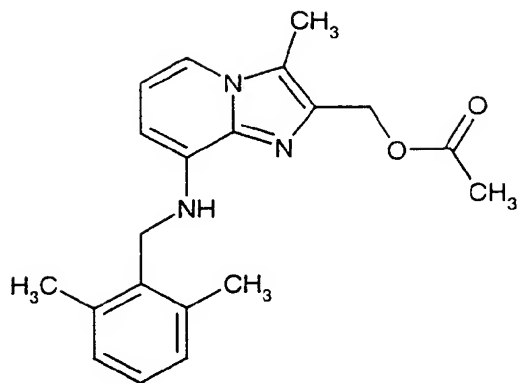
The filtrate and washings were combined and dried and the solvents were removed under reduced pressure. The residue was purified by column chromatography on silica gel using methylene chloride: methanol (9:1) as eluent. Treating the residue with acetonitrile and filtration gave 0.36 g (77%) of the title compound.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 2.35 (s, 6H), 2.4 (s, 6H), 4.35 (d, 2H), 4.45 (s, 2H), 5.25 (t, 1H), 6.1 (s, 1H), 7.0-7.2 (m, 4H)

Example 1.4

Synthesis of [8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methyl acetate

16

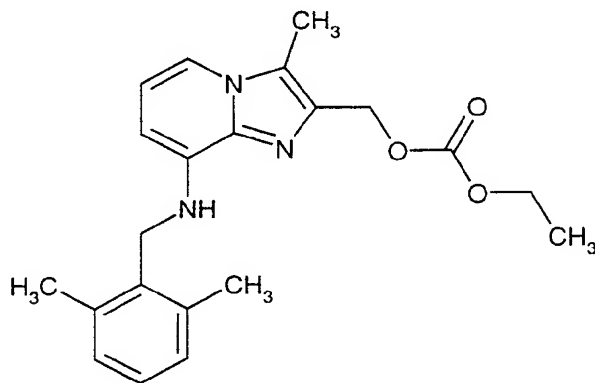


To a solution of 8-(2,6-dimethylbenzylamino)-2-hydroxymethyl-3-methylimidazo[1,2-a]pyridine (0.3 g, 1.0 mmol) and triethylamine (0.014 ml, 1.0 mmol) in methylene chloride (10 ml) was added dropwise acetyl chloride (0.071 ml, 1.0 mmol). The reaction mixture was stirred for 1.5 h. at room temperature. Water was added and the organic layer was separated, washed with sodium bicarbonate solution, dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using diethyl ether as eluent. Recrystallization from diethyl ether gave 0.16 g (47 %) of the desired product.

¹H-NMR (300 MHz, CDCl₃): δ 2.05 (s, 3H), 2.4 (s, 6H), 2.45 (s, 3H), 4.35 (d, 2H), 4.95 (bs, 1H), 5.2 (s, 2H), 6.25 (d, 1H), 6.8 (t, 1H), 7.05-7.2 (m, 3H), 7.3 (d, 2H)

Example 1.5

Synthesis of [8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methyl ethyl carbonate

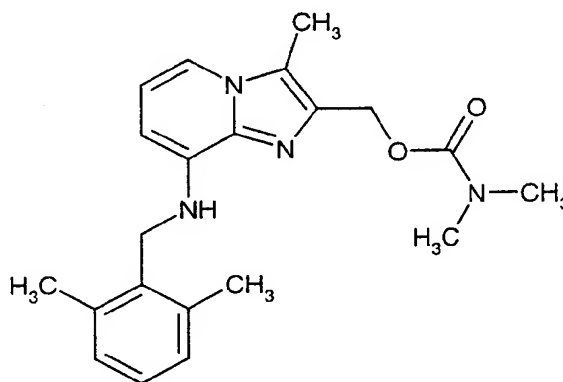


8-(2,6-dimethylbenzylamino)-2-hydroxymethyl-3-methylimidazo[1,2-a]pyridine (0.4 g, 1.3 mmol) and ethyl chloroformate (0.13 ml, 1.3 mmol) were solved in methylene chloride (20 ml) and were refluxed for 3 h. An additional amount of ethyl chloroformate (0.13 ml, 1.3 mmol) was added and the reaction mixture was refluxed 20 h. A sodium bicarbonate solution was added, the organic layer was separated dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using diethyl ether as eluent and crystallization from diethyl ether: petroleum ether (1:2) gave 0.11 g (23%) of the title compound.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.25 (t, 1H), 2.4 (s, 6H), 2.5 (s, 3H), 4.15 (q, 2H), 4.35 (d, 2H), 4.95 (bs, 1H), 5.25 (2H), 6.25 (d, 1H), 6.8 (t, 1H), 7.05-7.2 (m, 3H), 7.3 (d, 1H)

Example 1.6

Synthesis of [8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methyl *N,N*-dimethylcarbamate

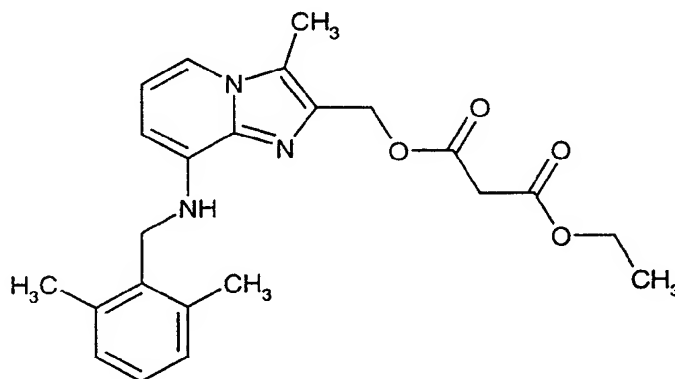


8-(2,6-dimethylbenzylamino)-2-hydroxymethyl-3-methylimidazo[1,2-a]pyridine (0.1 g, 0.34 mmol), dimethylcarbamyl chloride (0.03 ml, 0.34 mmol), sodium carbonate (0.1 g, 0.94 mmol) and a cat. amount of *N,N*-dimethylaminopyridine were added to acetonitrile (15 ml) and refluxed for 20 h. An additional amount of dimethylcarbamyl chloride (0.15 ml, 1.7 mmol) was added and the reaction mixture was refluxed for 24 h. The solids were removed by filtration and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate: petroleum ether (2:1) as eluent gave 0.07 g (56%) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 2.4 (s, 6H), 2.5 (s, 3H), 2.85 (d, 6H), 4.35 (d, 2H), 4.9 (bs, 1H), 5.2 (s, 2H), 6.25 (d, 1H), 6.75 (t, 1H), 7.05-7.15 (m, 3H), 7.3 (d, 1H)

Example 1.7

Synthesis of 1-[[8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methyl] 3-ethyl malonate



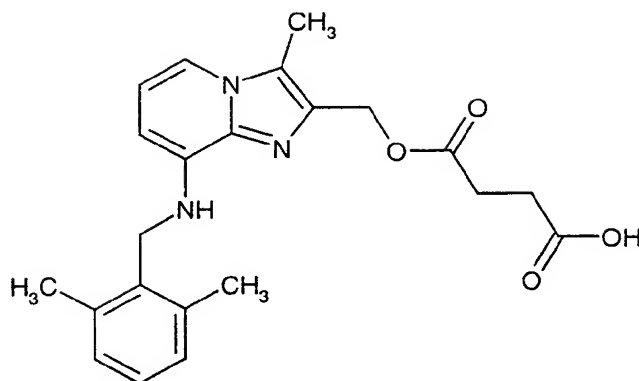
8-(2,6-dimethylbenzylamino)-2-hydroxymethyl-3-methylimidazo[1,2-a]pyridine (0.45 g, 1.5 mmol), ethyl malonyl chloride (0.23 g, 1.5 mmol) and sodium carbonate (0.32 g, 3.0 mmol) were added to methylene chloride (20 ml) and the mixture was stirred for 3 h. at room temperature. Water was added and the organic layer was separated, dried (Na₂SO₄) and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using diethyl ether as eluent and crystallization from petroleum ether gave 0.34 g (56 %) of the desired product.

¹H-NMR (300 MHz, CDCl₃): δ 1.2 (t, 3H), 2.4 (s, 6H), 2.55 (s, 3H), 3.4 (s, 2H), 4.15 (q, 2H), 4.35 (d, 2H), 4.9 (t, 1H), 5.25 (s, 2H), 6.25 (d, 1H), 6.8 (t, 1H), 7.05-7.15 (m, 3H), 7.35 (d, 1H)

Example 1.8

Synthesis of 4-[[8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methoxy]-4-oxobutanoic acid

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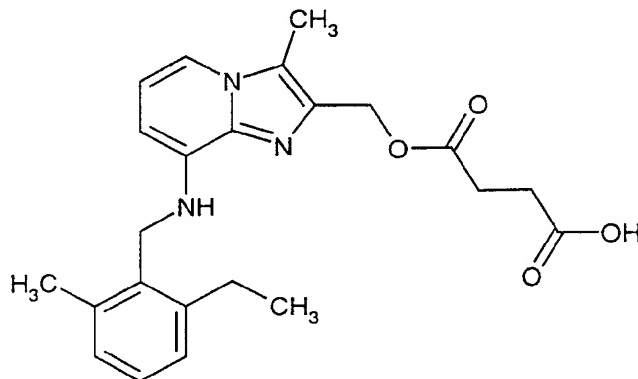


To a suspension of 8-(2,6-dimethylbenzylamino)-2-hydroxymethyl-3-methylimidazo[1,2-a]pyridine (0.2 g, 0.68 mmol) in acetonitrile (10 ml) was added sodium hydride (50% in oil) (0.036 g, 0.75 mmol) and the mixture was stirred for 5 min. To the mixture was added succinic anhydride (0.1 g, 1.0 mmol) and the reaction mixture was refluxed for 20 h. The solvent was evaporated under reduced pressure. To the residue was added water and the solid that formed was isolated by filtration and washed with acetonitrile to give 0.24 g (89 %) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 2.35-2.55 (m, 13H), 4.35 (s, 2H), 4.9 (bs, 2H), 5.2 (s, 2H) 6.25 (d, 1H), 6.8 (t, 1H), 7.0-7.1 (m, 3H), 7.25 (d, 1H)

Example 1.9

Synthesis of 4-[[8-(2-ethyl-6-methylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methoxy]-4-oxobutanoic acid



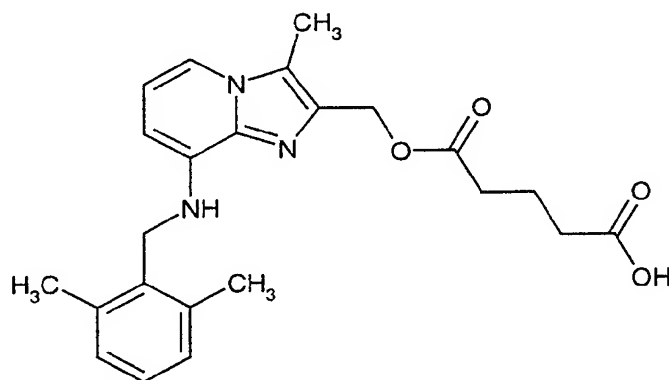
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To a suspension of 8-(2-ethyl-6-methylbenzylamino)-2-hydroxymethyl-3-methylimidazo[1,2-a]pyridine (0.47 g, 1.5 mmol) in acetonitrile (20 ml) was added sodium hydride (50% in oil) (0.081 g, 1.7 mmol) and the mixture was stirred for 5 min. To the mixture was added succinic anhydride (0.23 g, 2.3 mmol) and the reaction mixture was refluxed for 20 h. The solvent was evaporated under reduced pressure. The residue was suspended in water and the pH was adjusted to 6 with 2M HCl and the solid that formed was isolated by centrifuging. Washing with water and with acetonitrile gave 0.51 g, (82 %) of the desired product.

¹H-NMR (300 MHz, CDCl₃): δ 1.2 (t, 1H), 2.35-2.55 (m, 10H), 2.7 (q, 2H), 4.3 (s, 2H), 5.2 (s, 2H), 6.25 (d, 1H), 6.8 (t, 1H), 7.0-7.2 (m, 3H), 7.3 (d, 1H)

Example 1.10

Synthesis of 5-[[8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methoxy]-5-oxopentanoic acid

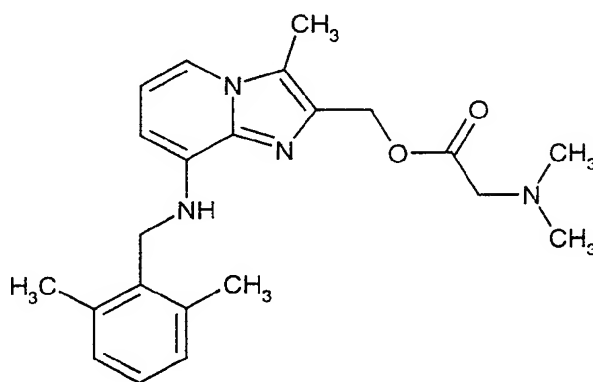


To a solution of 8-(2,6-dimethylbenzylamino)-2-hydroxymethyl-3-methylimidazo[1,2-a]pyridine (0.3 g, 1.0 mmol) in tetrahydrofuran (10 ml) was added sodium hydride (50% in oil) (0.054 g, 1.1 mmol) and the mixture was stirred for 10 min. To the mixture was added glutaric anhydride (0.13 g, 1.1 mmol) and the reaction mixture was refluxed for 20 h. The solvent was evaporated under reduced pressure. The residue was partitioned between dichloromethane and water. The pH was adjusted to 4 with 2M HCl. The organic layer was separated, dried (Na₂SO₄) and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using dichloromethane:methanol (94:6) as eluent gave 0.034 g (8 %) of the title compound.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.75 (t, 2H), 2.1 (t, 2H), 2.3 (t, 2H), 2.35 (s, 6H), 2.45 (s, 3H), 4.3 (s, 2H), 5.2 (s, 2H), 5.5 (bs, 1H), 6.25 (d, 1H), 6.8 (t, 1H), 7.0-7.15 (m, 3H), 7.3 (d, 1H)

5 *Example 1.11*

Synthesis of [8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methyl 2-(dimethylamino)acetate



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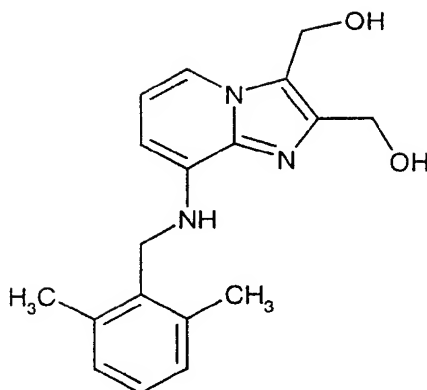
8-(2,6-dimethylbenzylamino)-2-chloromethyl-3-methylimidazo[1,2-a]pyridine (0.3 g, 1.0 mmol) and N,N-dimethylglycine (0.1 g, 1.0 mmol) were added to acetonitrile (10 ml) and the mixture was refluxed for 20 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel using
 15 dichloromethane:methanol (10:2) as eluent. Recrystallization from acetonitrile gave 0.12 g (32%) of the title compound

$^1\text{H-NMR}$ (300 MHz, CD_3OD): δ 2.4 (s, 6H) 2.55 (s, 3H), 3.25 (s, 6H), 3.85 (s, 2H), 4.4
 20 (s, 2H), 4.9 (s, 2H), 6.5 (d, 1H), 6.95 (t, 1H), 7.05-7.15 (m, 3H), 7.6 (d, 1H)

Example 1.12

Synthesis of 8-(2,6-dimethylbenzylamino)-2,3-dihydroxymethyl-imidazo[1,2-a]pyridine

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To an icecoole solution of diethyl 8-(2,6-dimethylbenzylamino)imidazo[1,2-a]pyridine-2,3-dicarboxylate (2.5 g, 6.3 mmol) in toluene (100 ml) was added Red-Al (14 ml, 45 mmol)(65 % in toluene) during 3 h. The temperature was allowed to raise to room temperature a Rochell salt solution (35 g potassium sodium tartrate in 250 ml H₂O) was added. The organic layer was separated dried and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using dichloromethane: isopropylalcohol (4:1) gave 0.09 g (5%) of de desired product

¹H-NMR (300 MHz, CDCl₃): δ 2.4 (s, 6H), 4.45 (s, 2H), 4.7 (s, 2H), 4.95 (s, 2H), 6.5 (d, 1H), 6.9 (t, 1H), 7.05-7.2 (m, 3H), 7.75 (d, 1H)

2. PREPARATION OF INTERMEDIATES

Example 2.1

Synthesis of ethyl 8-amino-3-methylimidazo[1,2-a]pyridin-2-carboxylate

A solution of 2,3-diaminopyridine (6.8 g, 62 mmol) and 3-bromo-2-oxo-butyric acid ethyl ester (13 g, 62 mmol) in 1,2-dimethoxyethane (150 ml) was refluxed for 2 h. Sodium carbonate (6.5 g, 62 mmol) was added and the mixture was refluxed for 2 h. The solids were isolated by filtration and washed with dichloromethane:methanol (10:1). The filtrate and washings were combined the solvents were removed under reduced pressure. The oily residue was washed with petroleum ether and was purified twice by column chromatography on silica gel using 1) dichloromethane:methanol (10:1) 2) ethyl acetate as eluent to give 4.6 g (34%) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 1.45 (t, 3H), 2.75 (s, H), 4.5 (q, 2H), 4.65 (bs, 2H), 6.35 (d, 1H), 6.7 (t, 1H), 7.35 (d, 1H)

Example 2.2

Synthesis of ethyl 8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-carboxylate

Ethyl 8-amino-3-methylimidazo[1,2-a]pyridin-2-carboxylate (4.6 g, 21 mmol), 2,6-dimethylbenzyl chloride (3.2 g, 21 mmol), sodium carbonate (4.4 g, 42 mmol) and a cat. amount of potassium iodide were added to acetonitrile (50 ml) and refluxed for 3 h. , stirred for 20 h. at room temperature and refluxed for 1 h. The solids were removed by filtration and the solvents were evaporated under reduced pressure. The residue was dissolved in methylene chloride and washed with water. The organic layer was separated, dried (Na₂SO₄) and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using methylene chloride:methanol (10:1) as eluent and crystallization from ethyl acetate gave 4.0 g (56%) of the desired product.

¹H-NMR (300 MHz, CDCl₃): δ 1.4 (t, 3H), 2.4 (s, 6H), 2.75 (s, 3H), 4.35 (d, 2H), 4.45 (q, 2H), 5.15 (t, 1H), 6.25 (d, 1H), 6.85 (t, 1H), 7.05-7.2 (m, 3H), 7.35 (d, 1H)

Example 2.3

Synthesis of ethyl 8-(2-ethyl-6-methylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-carboxylate

To a stirred mixture of ethyl 8-amino-3-methylimidazo[1,2-a]pyridin-2-carboxylate (1.53 g, 7.0 mmol) in methanol (25 ml) were added 2-ethyl-6-methylbenzaldehyde (1.1 g, 7.1 mmol), zinc(II)chloride (1.1 g, 8.0 mmol) in methanol (10 ml) and sodium cyanoborohydride (0.5 g, 8.0 mmol). The reaction mixture was refluxed for 4 h. and then stirred at room temperature for 20 h. Triethylamine (2.5 ml) was added and the mixture was stirred for 30 min. and evaporated under reduced pressure. Purification of the residue by column chromatography twice on silica gel using 1) methylene chloride:methanol (95:5) 2) heptane:isopropyl ether (1:5) as eluent gave 0.2 g (8 %) of the title compound.

^1H -NMR (300 MHz, CDCl_3): δ 1.25 (t, 3H), 1.4 (t, 3H), 2.4 (s, 3H), 2.65-2.8 (m, 5H), 4.35 (d, 2H), 4.45 (q, 2H), 5.15 (t, 1H), 6.25 (d, 1H), 6.85 (t, 1H), 7.05-7.2 (m, 3H), 7.35 (d, 1H)

5 *Example 2.4*

Synthesis of ethyl 8-amino-3,6-dimethylimidazo[1,2-a]pyridin-2-carboxylate

A solution of 2,3-diamino-5-methyl-pyridine (2.3 g, 19 mmol) and 3-bromo-2-oxo-butyric
10 acid ethyl ester (4.3 g, 21 mmol) in ethanol (25 ml) was refluxed for 20 h.. Sodium
carbonate (2.6 g, 25 mmol) was added and the mixture was filtrated and the solids were
washed with ethanol. The filtrate and washings were combined and evaporated under
reduced pressure. The residue was dissolved in methylene chloride, washed twice with a
sodium carbonate solution and twice with water. The organic layer was separated dried
15 (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column
chromatography on silica gel using methylene chloride:methanol (9:1) as eluent gave 1.3 g
(30 %) of the title compound as an oil.

^1H -NMR (300 MHz, CDCl_3): δ 1.4 (t, 3H), 2.25 (s, 3H), 2.7 (s, 3H), 4.45 (q, 2H), 4.75 (bs,
20 2H), 6.2 (s, 1H), 7.1 (s, 1H)

Example 2.5

Synthesis of ethyl 8-(2,6-dimethylbenzylamino)-3,6-dimethylimidazo[1,2-a]pyridin-2-
25 *-carboxylate*

Ethyl 8-amino-3,6-dimethylimidazo[1,2-a]pyridin-2-carboxylate (1.3 g, 5.6 mmol), 2,6-
dimethylbenzyl chloride (0.9 g, 6.2 mmol), potassium carbonate (1.5 g, 11 mmol) and
sodium iodide (0.1 g, 0.6 mmol) were added to acetonitrile (15 ml) and refluxed for 20 h.
30 The solvent was evaporated under reduced pressure. The residue was dissolved in
methylene chloride, washed twice with water and the organic layer was separated dried
(Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column
chromatography on silica gel using heptane:ethyl acetate (2:1) as eluent gave 0.9 g (47 %)
of the title compound as an oil.

¹H-NMR (300 MHz, CDCl₃): δ 1.35 (t, 3H), 2.4 (s, 3H), 2.45 (s, 6H), 2.7 (s, 3H), 4.35 (d, 2H), 4.4 (q, 2H), 5.05 (t, 1H), 6.1 (s, 1H), 7.05-7.2 (m, 4H)

Example 2.6

Synthesis of diethyl 8-aminoimidazo[1,2-a]pyridin-2,3-dicarboxylate

A solution of 2,3-diaminopyridine (13.1 g, 0.12 mol), 2-bromo-3-oxo-succinic acid diethyl ester (31 g, 0.12 mol) and sodium carbonate (13.2 g, 0.12 mol) in 1,2-dimethoxyethane (200 ml) was refluxed for 20 h. The solvent was evaporated under reduced pressure and the residue was suspended in methylene chloride and filtrated through silica gel. The filtrate was evaporated under reduced pressure to give 10.9 g (33%) of the title compound as an oil.

¹H-NMR (300 MHz, CD₃OD): δ 1.5 (t, 6H), 4.5 (q, 4H), 7.15 (d, 1H), 7.3 (t, 1H), 8.75 (d, 1H)

Example 2.7

Synthesis of diethyl 8-(2,6-dimethylbenzylamino)-imidazo[1,2-a]pyridin-2,3-dicarboxylate

Diethyl 8-aminoimidazo[1,2-a]pyridin-2,3-dicarboxylate (2.8 g, 10 mmol), 2,6-dimethylbenzyl chloride (1.9 g, 12 mmol), potassium carbonate (2.0 g, 15 mmol) and sodium iodide (0.22 g, 1.5 mmol) were added to acetonitrile (100 ml) and refluxed for 20 h.

Methylene chloride was added to the cooled reaction mixture and was washed with water. The organic layer was separated, dried (Na₂SO₄) and evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using methylene chloride as eluent gave 2.5 g (63%) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 1.3-1.45 (m, 6H), 2.35 (s, 6H), 4.3 (d, 2H), 4.35-4.45 (m, 4H), 5.05 (t, 1H), 6.45 (d, 1H), 6.95-7.15 (m, 4H), 8.55 (d, 1H)

Example 2.8

Synthesis of 8-(2,6-dimethylbenzylamino)-2-chloromethyl-3-methylimidazo[1,2-a]pyridine

To a solution of 8-(2,6-dimethylbenzylamino)-2-hydroxymethyl-3-methylimidazo[1,2-a]pyridine (1.0 g, 3.4 mmol) in methylene chloride (50 ml) was added dropwise thionyl chloride (0.5 g, 3.4 mmol) solved in methylene chloride (10 ml) at 5 °C. The reaction mixture was stirred 2 h. at 5 °C. To the mixture was washed with a saturated bicarbonate solution, the organic layer was separated, dried (Na₂SO₄) and evaporated under reduced pressure to give 1.0 g (93%) of the title compound.

¹H-NMR (300 MHz, CDCl₃): δ 2.4 (s, 6H), 2.5 (s, 3H), 4.35 (d, 2H), 4.75 (s, 2H), 4.9 (bs, 1H), 6.25 (d, 1H), 6.8 (t, 1H), 7.05-7.15 (m, 3H), 7.25 (d, 1H)

BIOLOGICAL TESTS

1. In vitro experiments

Acid secretion inhibition in isolated rabbit gastric glands

Inhibiting effect on acid secretion *in vitro* in isolated rabbit gastric glands was measured as described by Berglinde et al. (1976) Acta Physiol. Scand. 97, 401-414.

Determination of H⁺, K⁺-ATPase activity

Membrane vesicles (2.5 to 5 µg) were incubated for 15 min at +37°C in 18 mM Pipes/Tris buffer pH 7.4 containing 2 mM MgCl₂, 10 mM KCl and 2 mM ATP. The ATPase activity was estimated as release of inorganic phosphate from ATP, as described by LeBel et al. (1978) Anal. Biochem. 85, 86-89.

2. In vivo experiments

Inhibiting effect on acid secretion in female rats

Female rats of the Sprague-Dawley strain are used. They are equipped with cannulated fistulae in the stomach (lumen) and the upper part of the duodenum, for collection of gastric secretions and administration of test substances, respectively. A recovery period of 14 days after surgery is allowed before testing commenced.

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Before secretory tests, the animals are deprived of food but not water for 20 h. The stomach is repeatedly washed through the gastric cannula with tap water ($+37^{\circ}\text{C}$), and 6 ml Ringer-Glucose given subcutaneously. Acid secretion is stimulated with infusion during 2.5-4 h (1.2 ml/h, subcutaneously) of pentagastrin and carbachol (20 and 110 nmol/kg·h, respectively), during which time gastric secretions are collected in 30-min fractions. Test substances or vehicle are given either at 60 min after starting the stimulation (intravenous and intraduodenal dosing, 1 ml/kg), or 2 h before starting the stimulation (oral dosing, 5 ml/kg, gastric cannula closed). The time interval between dosing and stimulation may be increased in order to study the duration of action. Gastric juice samples are titrated to pH 7.0 with NaOH, 0.1 M, and acid output calculated as the product of titrant volume and concentration.

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Further calculations are based on group mean responses from 4-6 rats. In the case of administration during stimulation; the acid output during the periods after administration of test substance or vehicle are expressed as fractional responses, setting the acid output in the 30-min period preceding administration to 1.0. Percentage inhibition is calculated from the fractional responses elicited by test compound and vehicle. In the case of administration before stimulation; percentage inhibition is calculated directly from acid output recorded after test compound and vehicle.

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Bioavailability in rat

Adult rats of the Sprague-Dawley strain are used. One to three days prior to the experiments all rats are prepared by cannulation of the left carotid artery under anaesthesia. The rats used for intravenous experiments are also cannulated in the jugular vein (Popovic

30

(1960) J. Appl. Physiol. 15, 727-728). The cannulas are exteriorized at the nape of the neck.

Blood samples (0.1 - 0.4 g) are drawn repeatedly from the carotid artery at intervals up to
5 5.5 hours after given dose. The samples are frozen until analysis of the test compound.

Bioavailability is assessed by calculating the quotient between the area under blood/plasma concentration (AUC) curve following (i) intraduodenal (i.d.) or oral (p.o.) administration and (ii) intravenous (i.v.) administration from the rat or the dog, respectively.

10

The area under the blood concentration vs. time curve, AUC, is determined by the log/linear trapezoidal rule and extrapolated to infinity by dividing the last determined blood concentration by the elimination rate constant in the terminal phase. The systemic bioavailability (F%) following intraduodenal or oral administration is calculated as

15

$F(\%) = (AUC \text{ (p.o. or i.d.)} / AUC \text{ (i.v.)}) \times 100.$

Inhibition of gastric acid secretion and bioavailability in the conscious dog.

Labrador retriever or Harrier dogs of either sex are used. They are equipped with a
20 duodenal fistula for the administration of test compounds or vehicle and a cannulated gastric fistula or a Heidenhaim-pouch for the collection of gastric secretion.

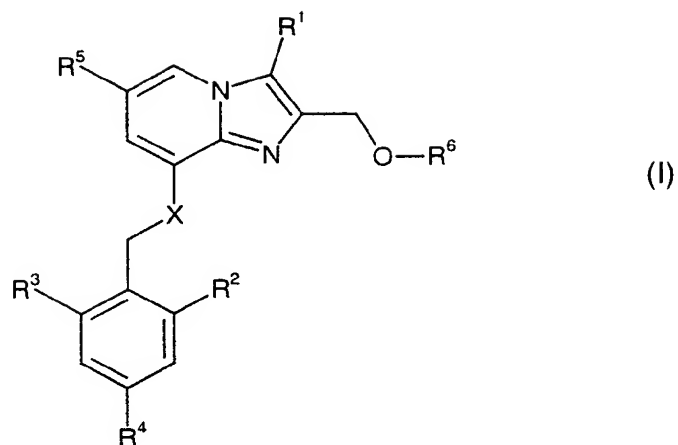
Before secretory tests the animals are fasted for about 18 h but water is freely allowed. Gastric acid secretion is stimulated for up to 6.5 h infusion of histamine dihydrochloride
25 (12 ml/h) at a dose producing about 80% of the individual maximal secretory response, and gastric juice collected in consecutive 30-min fractions. Test substance or vehicle is given orally, i.d. or i.v., 1 or 1.5 h after starting the histamine infusion, in a volume of 0.5 ml/kg body weight. In the case of oral administration, it should be pointed out that the test compound is administered to the acid secreting main stomach of the Heidenham-pouch
30 dog.

The acidity of the gastric juice samples are determined by titration to pH 7.0, and the acid output calculated. The acid output in the collection periods after administration of test substance or vehicle are expressed as fractional responses, setting the acid output in the fraction preceding administration to 1.0. Percentage inhibition is calculated from fractional responses elicited by test compound and vehicle.

Blood samples for the analysis of test compound concentration in plasma are taken at intervals up to 4 h after dosing. Plasma is separated and frozen within 30 min after collection and later analyzed. The systemic bioavailability (F%) after oral or i.d. administration is calculated as described above in the rat model.

CLAIMS

1. A compound of the formula I



or a pharmaceutically acceptable salt thereof, wherein

10 R^1 is
 (a) H,
 (b) CH_3 , or
 (c) CH_2OH ;

15 R^2 is C_1 - C_6 alkyl;

R^3 is C_1 - C_6 alkyl;

20 R^4 is
 (a) H, or
 (b) halogen;

25 R^5 is
 (a) H, or
 (b) C_1 - C_6 alkyl;

.R⁶ is

- (a) H,
- (b) C₁-C₆ alkyl carbonyl

5 (c) C₃-C₇ cycloalkyl carbonyl, in which the cycloalkyl group is optionally substituted by one or more substituents selected from, C₁-C₆ alkyl, C₁-C₆ alkoxy, -COOH or -COO-(C₁-C₆) alkyl

10 (d) Aryl C₁-C₆ alkyl carbonyl, in which aryl represents phenyl, pyridyl, thienyl or furanyl, optionally substituted by one or more substituents selected from, C₁-C₆ alkyl, C₁-C₆ alkoxy, -COOH or -COO-(C₁-C₆) alkyl

(e) C₁-C₆ alkoxy C₁-C₆ alkyl carbonyl

15 (f) C₁-C₆ alkoxy carbonyl

(g) aryl carbonyl, in which aryl represents phenyl, pyridyl, thienyl or furanyl, optionally

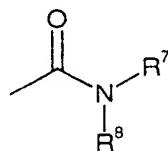
substituted by one or more substituents selected from, C₁-C₆ alkyl, C₁-C₆ alkoxy, -COOH or -COO-(C₁-C₆) alkyl

20 (h) C₃-C₇ cycloalkyl C₁-C₆ alkylcarbonyl, in which the cycloalkyl group is optionally substituted by one or more substituents selected from, C₁-C₆ alkyl, C₁-C₆ alkoxy, -COOH or -COO-(C₁-C₆) alkyl

25 (i) C₁-C₆ alkoxy C₁-C₆ alkoxy carbonyl

(j) C₁-C₆ alkoxy C₁-C₆ alkoxy C₁-C₆ alkylcarbonyl

30 (k) a carbamoyl group with the formula



wherein R^7 , R^8 are the same or different and are H, or C_1 - C_6 alkyl

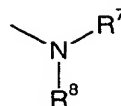
(l) R^9 -(C_1 - C_6) alkylcarbonyl

5 wherein R^9 is

$HOC=O$ -, C_1 - C_6 alkyl- $O-C=O$ -, or

an aminogroup with the formula

10



wherein R^7 , R^8 are the same or different and are H, or C_1 - C_6 alkyl

(m) R^9 -hydroxylated-(C_1 - C_6) alkylcarbonyl

15

(n) R^9 -(C_1 - C_6) alkenylcarbonyl

X is

(a) NH, or

20

(b) O.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

R^1 is

(a) CH_3 , or

25

(b) CH_2OH ;

R^2 is C_1 - C_6 alkyl;

R^3 is C_1 - C_6 alkyl;

30

R^4 is

(a) H, or

(b) halogen;

.R⁵ is

- (a) H, or
- (b) C₁-C₆ alkyl;

5

R⁶ is

- (a) C₁-C₆ alkyl carbonyl

10

(b) C₃-C₇ cycloalkyl carbonyl, in which the cycloalkyl group is optionally substituted by one or more substituents selected from, C₁-C₆ alkyl, C₁-C₆ alkoxy, -COOH or -COO-(C₁-C₆) alkyl

15

(c) Aryl C₁-C₆ alkyl carbonyl, in which aryl represents phenyl, pyridyl, thienyl or furanyl, optionally substituted by one or more substituents selected from, C₁-C₆ alkyl, C₁-C₆ alkoxy, -COOH or -COO-(C₁-C₆) alkyl

- (d) C₁-C₆ alkoxy C₁-C₆ alkyl carbonyl

- (e) C₁-C₆ alkoxy carbonyl

20

(f) aryl carbonyl, in which aryl represents phenyl, pyridyl, thienyl or furanyl, optionally substituted by one or more substituents selected from, C₁-C₆ alkyl, C₁-C₆ alkoxy, -COOH or -COO-(C₁-C₆) alkyl

25

(g) C₃-C₇ cycloalkyl C₁-C₆ alkylcarbonyl, in which the cycloalkyl group is optionally substituted by one or more substituents selected from, C₁-C₆ alkyl, C₁-C₆ alkoxy, -COOH or -COO-(C₁-C₆) alkyl

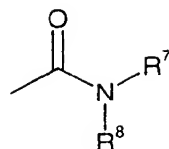
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- (h) C₁-C₆ alkoxy C₁-C₆ alkoxycarbonyl

- (i) C₁-C₆ alkoxy C₁-C₆ alkoxy C₁-C₆ alkylcarbonyl

- (j) a carbamoyl group with the formula

35



wherein R^7 , R^8 are the same or different and are H, or C_1 - C_6 alkyl

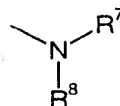
5 (k) R^9 -(C_1 - C_6) alkylcarbonyl

wherein R^9 is

HOC=O-, C_1 - C_6 alkyl-O-C=O-, or

10

an aminogroup with the formula



15

wherein R^7 , R^8 are the same or different and are H, or C_1 - C_6 alkyl

(l) R^9 -hydroxylated-(C_1 - C_6) alkylcarbonyl

(m) R^9 -(C_1 - C_6) alkenylcarbonyl

20

X is

(a) NH, or

(b) O.

25 3. A compound according to claim 1, or a pharmaceutically acceptable salt thereof,

wherein R^1 is CH_3 or CH_2OH ; R^2 is CH_3 or CH_2CH_3 ; R^3 is CH_3 or CH_2CH_3 ; R^4 is H,

Br, Cl or F; R^5 is H or CH_3 .

[8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methyl acetate;

30 [8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methyl ethyl carbonate;

[8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methyl N,N-dimethylcarbamate;

1-[[8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methyl] 3-ethyl malonate;

5 4-[[8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methoxy]-4-oxobutanoic acid;

4-[[8-(2-ethyl-6-methylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methoxy]-4-oxobutanoic acid;

10 5-[[8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methoxy]-5-oxopentanoic acid;

[8-(2,6-dimethylbenzylamino)-3-methylimidazo[1,2-a]pyridin-2-yl]methyl 2-(dimethylamino)acetate;

or a pharmaceutically acceptable salt thereof.

15 4. 8-(2,6-dimethylbenzylamino)-2,3-dihydroxymethyl-imidazo[1,2-a]pyridine;
8-(2-ethyl-6-methylbenzylamino)-2-hydroxymethyl-3-methylimidazo[1,2-a]pyridine;
8-(2,6-dimethylbenzylamino)-2-hydroxymethyl-3-methylimidazo[1,2-a]pyridine;
8-(2,6-dimethylbenzylamino)-3,6-dimethyl-2-hydroxymethylimidazo[1,2-a]pyridine;

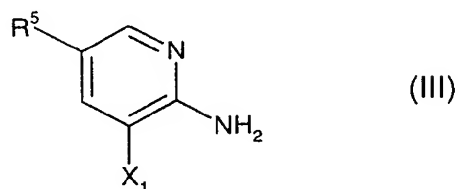
20 or a pharmaceutically acceptable salt thereof.

5. Products containing a compound according to any of claims 1-4 and at least one antimicrobial agent as a combined preparation for simultaneous, separate or sequential
25 use in the prevention or treatment of gastrointestinal inflammatory diseases.

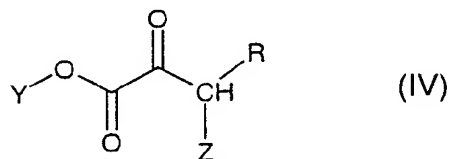
6. Products containing a compound according to any of claims 1-4 and at least one proton pump inhibitor as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of gastrointestinal inflammatory diseases.

30 7. A process for the preparation of a compound according to any one of claims 1 to 4, comprising;

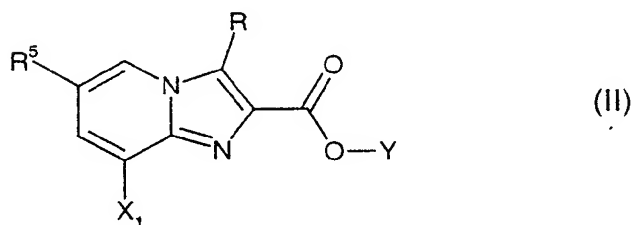
a) reacting a compound of the general Formula III



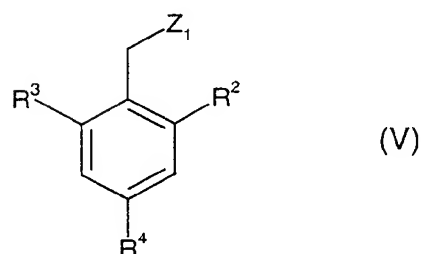
5 wherein X1 is NH₂ or OH and R⁵ is as defined for Formula I, with compounds of the general Formula IV



10 wherein Z is a leaving group, Y is a lower alkyl group and R is H, CH₃ or an ester group in an inert solvent under standard conditions to compounds of the Formula II

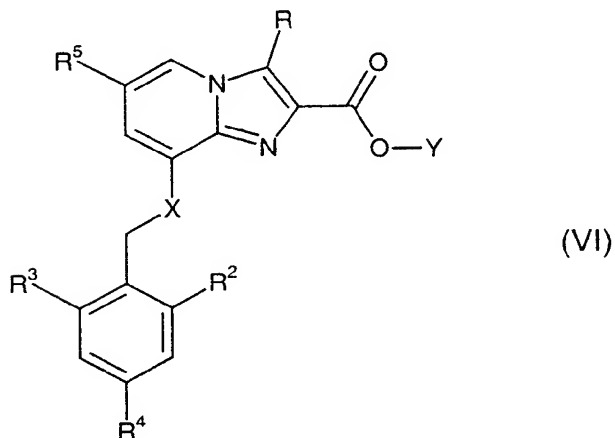


15 b) reacting compounds of the general Formula V



wherein R^2 , R^3 and R^4 are as defined for Formula I and Z1 is a leaving group, with compounds of the Formula II under standard conditions in an inert solvent with or without a base, to compounds of Formula VI

5



wherein R^2 , R^3 , R^4 , R^5 and X are as defined for Formula I, Y is a lower alkyl group and R is H, CH_3 or an ester group.

10

c) Reducing compounds of the general Formula VI in an inert solvent to compounds of the general Formula I wherein R^6 is H.

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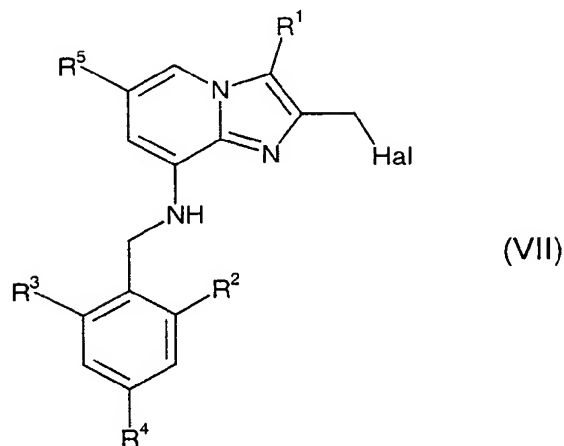
d) Introducing the substituent R^6 of Formula I ($R^6 \neq H$) by standard acylating procedures by reacting compounds of the Formula I wherein R^6 is H, with the acid, acid halide or the anhydride of R^6 ($R^6 \neq H$).

5. A process for the preparation of a compound according to any of claims 1 to 4 comprising;

20

a) halogenation of the hydroxymethyl group in compounds of the Formula I wherein R^6

is H to the corresponding halogenmethyl group of Formula VII by standard methods.



- 5 b) Introducing R^6 of Formula I ($R^6 \neq H$) by reacting compounds of Formula VII with the corresponding acid of R^6 ($R^6 \neq H$) under standard conditions.
6. A compound according to any one of claims 1 to 4 for use in therapy.
- 10 7. A pharmaceutical formulation containing a compound according to any one of claims 1 to 4 as active ingredient in combination with a pharmaceutically acceptable diluent or carrier.
8. Use of a compound according to any one of claims 1 to 4 for the manufacture of a

15 medicament for the inhibition of gastric acid secretion.
9. Use of a compound according to any one of claims 1 to 4 for the manufacture of a medicament for the treatment of gastrointestinal inflammatory diseases.
- 20 10. Use of a compound according to any one of claims 1 to 4 the manufacture of a medicament for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, wherein the said salt is adapted to be

administered in combination with at least one antimicrobial agent.

11. A method for inhibiting gastric acid secretion which comprises administering to a mammal, including man, in need of such inhibition an effective amount of a compound according to any one of claims 1 to 4.
12. A method for the treatment of gastrointestinal inflammatory diseases which comprises administering to a mammal, including man, in need of such treatment an effective amount of a compound according to any one of claims 1 to 4.
13. A method for the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, which comprises administering to a mammal, including humans, in need of such treatment an effective amount of a compound as claimed in any one of claims 1 to 4, wherein the said salt is administered in combination with at least one antimicrobial agent.
14. A pharmaceutical formulation for use in the inhibition of gastric acid secretion wherein the active ingredient is a compound according to any one of claims 1 to 4.
15. A pharmaceutical formulation for use in the treatment of gastrointestinal inflammatory diseases wherein the active ingredient is a compound according to any one of claims 1 to 4.
16. A pharmaceutical formulation for use in the treatment or prophylaxis of conditions involving infection by *Helicobacter pylori* of human gastric mucosa, wherein the active ingredient is a compound according to any one of claims 1 to 4 in combination with at least one antimicrobial agent.



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(21) International Application Number: PCT/DK99/00480 (22) International Filing Date: 10 September 1999 (10.09.99) (30) Priority Data: PA 1998 01143 10 September 1998 (10.09.98) DK (71) Applicant (for all designated States except US): NYCOMED DANMARK A/S [DK/DK]; Langebjerg 1, Postboks 88, DK-4000 Roskilde (DK). (72) Inventors; and (75) Inventors/Applicants (for US only): BERTELSEN, Poul [DK/DK]; Duevej 42, 4.th., DK-2000 Frederiksberg (DK). HANSEN, Nils, Gjerløv [DK/DK]; Kr. Zahrtmanns Plads 76, 1, DK-2000 Frederiksberg (DK). RUCKENDORFER, Hermann [AT/AT]; Reichenthal 170, A-4193 Reichenthal (AT). ITAI, Shigeru [JP/JP]; 403-21, 1-chome, Ageo-shi, Saitama 362-0046 (JP). (74) Agent: PLOUGMANN, VINGTOFT & PARTNERS A/S; Sankt Annæ Plads 11, P.O. Box 3007, DK-1021 Copen- hagen K (DK).		(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the</i> <i>claims and to be republished in the event of the receipt of</i> <i>amendments.</i>
(54) Title: QUICK RELEASE PHARMACEUTICAL COMPOSITIONS OF DRUG SUBSTANCES		
(57) Abstract <p>The present invention relates to an oral modified release pharmaceutical composition for the administration of a therapeutically and/or prophylactically effective amount of an active substance (a drug substance) to obtain a relatively fast or quick onset of the therapeutic and/or prophylactic effect. The drug substances contained in a modified release pharmaceutical composition according to the invention are suitably a drug substance which has a very low solubility under acidic conditions, i.e. under conditions similar to those present in the stomach and/or drug substances which have a pK_a value below about 5.5 such as in a range of from about 4 to about 5. The composition is based on a powder comprising a therapeutically and/or prophylactically active substance and has such a particle size that: when the powder is subjected to a sieve analysis, then at least about 90 % w/w of the particles passes through sieves 180 μm and the powder is contacted with an aqueous medium to form a particulate composition, which has such a particle size that when the particulate composition is subjected to a sieve analysis, then at least about 50 % w/w of the particles passes through sieve 180 μm. Furthermore, the composition, when tested in accordance with the dissolution method (I) defined herein employing 0.07 N hydrochloric acid as dissolution medium, releases at least about 50 % w/w of the active substance within the first 20 min of the test.</p>		

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QUICK RELEASE PHARMACEUTICAL COMPOSITIONS OF DRUG SUBSTANCES

The present invention relates to an oral modified release pharmaceutical composition for the administration of a therapeutically and/or prophylactically effective amount of an active substance (a drug substance) to obtain a relatively fast or quick onset of the therapeutic and/or prophylactic effect. The drug substances contained in a modified release pharmaceutical composition according to the invention are suitably a drug substance which has a very low solubility under acidic conditions, i.e. under conditions similar to those present in the stomach and/or drug substances which have a pK_a value below about 5.5 such as in a range of from about 4 to about 5. The compositions have been designed in such a manner that two important requirements are obtained, namely i) that the pharmaceutical composition releases the drug substance very fast under acidic conditions whereby the drug substance will become dissolved and, accordingly, available for absorption already almost immediately upon entrance into the stomach, and ii) that the mechanical strength of a composition according to the invention is sufficiently high to withstand normal handling of a pharmaceutical composition and to enable the composition to be coated using traditional coating equipment well known by a person skilled in the art. A composition according to the invention is suitable for use in those cases in which a fast onset of a therapeutic and/or prophylactic effect is desired, e.g. in connection with acute pain or mild to moderate pain. Accordingly, suitable therapeutically and/or prophylactically active substances may *inter alia* be found in the class of drug substances denoted non-steroid anti-inflammatory drug substances (abbreviated in the following: NSAID substances or NSAIDs).

DESCRIPTION OF THE INVENTION

Pharmaceutical compositions designed to immediate release of a drug substance is known in the art.

Generally, however, the rationale which lies behind the kind of compositions which have been described to enable an immediate release of a drug substance is to employ a traditional formulation approach (such as, e.g., i) plain tablets which have a disintegration time in water of at the most about 30 min, ii) a traditionally formulated granulate or iii) loose powder of the drug substance itself. By doing so the immediate release part of the composition is intended to release the drug substance in a manner which corresponds to

- a plain tablet formulation or the like and the term "immediate" is in such a context intended to denote that the release of the drug substance is faster than the release from a sustained release composition. The development of the so-called SplashDose®, FlashDose® and Flashtabs® are examples of pharmaceutical compositions wherein the
- 5 focus has been to obtain a very fast disintegration time. Such formulations are suitable for use for drug substances which are readily soluble in the gastro-intestinal tract, but basically they do not solve the problems related to drug substances which have poor solubility characteristics.
- 10 Especially in those cases where the drug substance has a low solubility in an acidic medium having a pH of from about 1 to about 3, i.e. a pH corresponding to the pH in the stomach, the traditional formulation approach will lead to a pharmaceutical composition which has a suitable fast disintegration time but not necessarily a suitable fast dissolution rate of the drug substance under acidic conditions, i.e. a plain tablet will rapidly
- 15 disintegrates into granules but the dissolution of the drug substance from the composition and/or the disintegrated composition under acidic conditions may be unsuitable low due to the solubility properties of the drug substance itself. The availability of a drug substance with respect to absorption, i.e. entrance into the circulatory system, is dependant on the presence of the drug substance on dissolved form as it is generally accepted that only
- 20 dissolved substances are capable of passing the mucous membranes in the gastro-intestinal tract. Therefore, it is important that the dissolution of the drug substance is suitably fast even under acidic conditions in order to enable a fast and initial absorption so that a true fast or immediate therapeutic response is obtainable.
- 25 For drug substances which are weak acids it is very important to ensure a proper bioavailability of the drug substance already under acid conditions in order to achieve a true rapid therapeutic effect. However, the various approaches disclosed with respect to achievement of a combination of a rapid effect do not seem to take all the above-mentioned factors into account and, hence, there is a need for developing compositions
- 30 which enable a true rapid onset of the therapeutic effect. To this end, we have especially focused on compositions comprising a drug substance belonging to the class of drug substances normally denoted NSAIDs, but other drug substances having a low solubility in acidic medium and/or a pK_a below about 5.5 may as well be suitable for use in a composition according to the invention.

Moreover, patients suffering from acute pain, mild to moderate pain and/or inflammatory conditions and/or related conditions very often require a dosage and a formulation which enable a fast onset of the therapeutic effect of the NSAID substances. The release from the dosage form must be safe, predictable and reliable. Furthermore, from a technical point of view, the release rate and the release pattern of the active drug substance from the composition should not significantly change during the shelf-life of the composition. A change in the release rate and/or release pattern may have a significant impact on the *in vivo* performance of the composition.

- 10 When testing prior art compositions intended for rapid release of the active drug substance (see e.g. Japanese patent No. 33491/90) the present inventors have revealed problems with respect to the release rate obtained and the robustness of the tablets. Thus, the development of a pharmaceutical composition which is suitable for rapid release of the active substance seems surprisingly to be a balance of on the one hand to obtain a composition which is sufficient robust to withstand normal handling (i.e. to have a sufficient mechanical strength) and on the other hand to enable a fast release and dissolution of the active drug substance in an acidic aqueous medium.

Thus, the purpose of the present invention is to provide a pharmaceutical composition for oral use which is useful for a fast delivery of an active drug substance to the circulatory system upon administration.

In one aspect, the invention relates to a quick release pharmaceutical composition for oral administration comprising a therapeutically and/or prophylactically active substance which has a solubility of at the most about 0.1 % w/v in 0.1 N hydrochloric acid at room temperature,

the composition being based on a powder comprising the therapeutically and/or prophylactically active substance and having such a particle size that - when the powder is subjected to a sieve analysis - then at least about 90% w/w such as, e.g. at least about 92% w/w, at least about 94% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 97% w/w, at least about 98% w/w or at least about 99% w/w of the particles passes through sieve 180 μ m, the powder being contacted with an aqueous medium to form a particulate composition, which has such a particle size that - when the particulate composition is subjected to a sieve analysis - then at least about

50% w/w such as, e.g., at least about 55% w/w, at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w or at least about 95% w/w of the particles passes through sieve 180 μ m, and

5

the composition - when tested in accordance with the dissolution method I defined herein employing 0.07 N hydrochloric acid as dissolution medium - releases at least about 50% w/w of the active substance within the first 20 min of the test.

10 In another aspect the invention relates to a quick release pharmaceutical composition for oral administration comprising a therapeutically and/or prophylactically active substance which has a solubility of at the most 0.1 % w/v in 0.1 N hydrochloric acid at room temperature,

15 the composition being in the form of a particulate composition or being based on a particulate composition which is obtained by contacting a powder comprising the therapeutically and/or prophylactically active substance with an aqueous medium in such a manner that the mean particle size of the particles of the particulate composition is at the most about 100% larger than the mean particle size of the powder before contact with
20 the aqueous medium, and

the composition - when tested in accordance with the dissolution method I defined herein employing 0.07 N hydrochloric acid as dissolution medium - releases at least about 50% w/w of the active substance within the first 20 min of the test.

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In preferred embodiments, the composition releases at least 55% w/w such as, e.g., at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 98% w/w
30 or at least about 99% w/w of the total active drug substance present in the composition within the first 20 min of the test.

In another aspect the invention relates to a method for the preparation of a composition according to the invention, the method comprising the steps of

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- i) mixing the therapeutically and/or prophylactically active substance with a) an alkaline substance, b) a filler having binding properties, and, optionally, c) other pharmaceutically acceptable excipients to obtain a powder mixture,
- 5 ii) contacting the thus obtained powder mixture with an aqueous medium to obtain a wet powder,
- iii) drying the thus obtained wet powder at a temperature above room temperature until the water content in the powder is at the most about 5% w/w determined as
10 described herein, to obtain a first particulate mixture,
- iv) sieving the thus obtained first particulate mixture,
- v) optionally, adding any further pharmaceutically acceptable excipients to obtain a
15 second particulate mixture,
- vi) optionally, compressing the thus obtained second particulate mixture into tablets, and
- 20 vii) optionally, coating the thus obtained tablets.

In still further aspects the invention relates to a method for treatment and/or prophylaxis of acute pain and/or mild or moderate pain comprising administering to a patient an effective amount of a therapeutically and/or prophylactically active drug substance in the form a
25 quick release composition according to the invention.

As mentioned above, the solubility of the therapeutically and/or prophylactically active substance in 0.1 N hydrochloric acid at room temperature is at the most about 0.1% w/v such as, e.g., at the most about 0.05% w/v, at the most about 0.01% w/v, at the most
30 about 0.009% w/v, at the most about 0.008% w/v, at the most about 0.007% w/v, at the most about 0.006% w/v, at the most about 0.005% w/v, at the most about 0.004% w/v, at the most about 0.003% w/v, at the most about 0.002 % w/v or at the most about 0.001% w/v.

Since the solubility of the therapeutically and/or prophylactically active substance such as, e.g., lornoxicam is $< 1 \text{ mg} / 100 \text{ ml}$ in 0.1 N HCl (aqueous solution of 0.1 N hydrochloric acid) the present inventors have found that incorporation of e.g. an NSAID substance in free form or in the form of a traditional formulation does not give the desired quick release under acidic conditions to enable a fast onset of the therapeutic effect *in vivo*.

Furthermore, irrespective of the solubility under acidic conditions, a composition containing an active drug substance which has a very low dissolution rate in 0.1 N or 0.07 N HCl may also present problems with respect to obtaining a quick release and dissolution of the active drug substance. Accordingly, compositions according to the invention may as well contain a therapeutically and/or prophylactically active substance which – when tested by solubility method I described herein – has such a dissolution rate that it allows an amount of at the most $50\% \text{ w/w}$ of the active substance to be dissolved within the first 20 min of the test.

A quick release of an active drug substance (such as, e.g., an NSAID substance) will, however, take place under acidic conditions provided that the drug substance is presented in a formulation wherein specific means has been used in order to manipulate the release rate so that the release becomes much faster compared to a traditional composition. Thus, the present inventors have found it necessary to adjust the release rate from a traditional composition when the active drug substance either has i) a very low solubility in 0.1 N hydrochloric acid, ii) a very low solubility rate, or iii) has a pK_a below about 5.5 such as, e.g., at the most about 5.3 , at the most about 5.2 , at the most about 5.0 such as, e.g., in a range of from about 3.4 to about 5.0 , in a range of from about 4.0 to about 5.0 . Thus, a fast release composition must be manipulated with respect to release in order to achieve a suitable fast release rate.

The present inventors have surprisingly found that in order to obtain a quick release composition containing active drug substances like the ones described above it is necessary to subject the active drug substance to contact with an alkaline substance under certain conditions. Furthermore, the success of the manufacture, i.e. a tablet that fulfils the general requirements of tablets, depends not only on a sole addition of e.g. sodium hydrogencarbonate (as described in Japanese patent No. 33491/90, Taisho) but also on the following parameters:

1. Contact conditions for the active drug substance and an alkaline substance (contact time, energy input and contact medium)
2. Inclusion of a substance denoted "a filler having binding properties"
3. The mean particle size of the filler having binding properties
- 5 4. The mean particle size or the particle size (as obtained from a sieve analysis) of the particulate material obtained after contacting the active drug substance and the alkaline substance with an aqueous medium and before any manufacture of the composition into e.g. tablets
- 10 5. The porosity of the particles obtained after contacting the active drug substance and the alkaline substance with an aqueous medium and before any manufacture of the composition into e.g. tablets. The present inventors have found that in certain cases it is possible to obtain suitable release characteristics even if the particle size is not as small as claimed. In those cases, however, the porosity of the particles has been sufficiently high to allow a quick release or alternatively, the hardness of the
- 15 particles is low.

In the experimental section herein is shown the influence of various process parameters on the properties of the resulting composition. The overall conclusion from the experiments is that in order to obtain a quick release composition it is of utmost importance to control conditions under which the contact between the active drug substance and the alkaline substance takes place. Furthermore, it is demonstrated that in order to obtain a composition with favourable shelf-life it seems necessary that the contact takes place during the manufacturing of the composition (see Example 12 which shows that when the contact between the active drug substance and the alkaline substance has taken place before manufacturing then a decreased shelf-life is obtained). Further investigations have shown that a suitable release is only obtained when the particle size of the particulate material obtained after contact between the active drug substance and the alkaline substance is controlled. (However, as explained above, the particle size requirement can be less stringent if the porosity of the particulate material is increased or if the hardness of the particles is decreased) In other words, it is of utmost importance with respect to the release of the active substance to ensure that the contact *in situ* between the active drug substance and the alkaline substance takes place under controlled conditions. The contact is performed by adding an aqueous medium to a powder mixture comprising the active drug substance and the alkaline substance and, optionally the filler having binding properties and other pharmaceutically acceptable

excipients. The addition of such a medium is performed by the same procedures as if the powder mixture is subjected to a wet granulation process. However, the present inventors have found that the application of the aqueous medium and the process involved must be controlled in such a manner that the resulting particulate mixture is not a traditional granulate, i.e. agglomerates built up of particles of the substances employed. Normally, during a granulation process the particle size is increased by a factor of at least 1.5 and a 200-500% increase may be observed. However, if agglomerates are formed to a major extent, the mean particle size of the particulate mixture will become so large that it has a negative impact on the release rate.

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Furthermore, the constitution of the aqueous medium is an important and critical factor (see below).

As a consequence of the above-mentioned formulation requirements, the present inventors have found that the manufacture of a composition according to the invention – even if a wetting step is included – is to be regarded as a process suitable for dry granulation and/or dry compression. It is contemplated that the balance between the qualities of the excipients and the aqueous treatment of the active substance and the alkaline substance is very important in order to obtain a suitable result with respect to both obtaining a quick release and a proper, substantially robust composition. It is believed that a mere effervescent tablet containing e.g. the active substance and sodium hydrogen carbonate will not lead to a controlled quick release because the carbon dioxide formed when such a tablet is dissolved in a glass of water will lead to a quick disintegration but not a quick dissolution. Most likely, the disintegration is so quick that the individual components (e.g. the active substance and the alkaline substance) have no substantial influence on one another. By subjecting the active substance and the alkaline substance to a controlled aqueous treatment, the formation of carbon dioxide during this treatment is believed to take place to some extent but the gas formation is not exhausted. Thus, when the tablet disintegrates in the stomach the remaining carbon dioxide is formed which allows a more ideal disintegration of the tablet and, consequently, gives rise to a local condition in the stomach which is favourable for quick dissolution of the active substance. A local increase in the pH value in the microenvironment of the particles is thus contemplated.

A composition according to the invention may be in the form of a solid composition such as in the form of a particulate composition or in the form of a unit dosage composition such as, e.g., a tablet, a capsule, a sachet or the like.

- 5 As mentioned above, the process with respect to the preparation of a composition according to the invention has to be controlled. Thus, it is important that the active drug substance is brought into contact with an alkaline substance. The alkaline substance may be an antacid or an antacid-like substance such as, e.g., sodium hydrogen carbonate, sodium carbonate, potassium carbonate, magnesium carbonate, magnesium hydroxide or
- 10 magnesium metasilicate aluminate or mixtures thereof. The reaction medium is typically a solvent comprising water and an organic solvent. The organic solvent is a solvent which is miscible with water such as, e.g., a branched or unbranched lower (C_1 - C_5) aliphatic alcohol like, e.g., ethanol, methanol, isopropanol, 1-propanol, 1-butanol, 2-butanol, tert. butanol, 1-pentanol, 2-pentanol, 3-pentanol, iso-pentanol and tert. pentanol and mixtures
- 15 thereof.

The concentration of the organic solvent in the solvent employed is normally from about 0% v/v to about 95% v/v such as, e.g., from about 10% v/v to about 90% v/v, from about 10% v/v to about 80% v/v, from about 15% v/v to about 70% v/v, from about 15% v/v to

20 about 60% v/v, from about 20% v/v to about 50% v/v, from about 20% v/v to about 40% v/v, from about 25% v/v to about 30% v/v such as, e.g. about 25% v/v.

An especially suitable organic solvent is ethanol in a concentration from about 0% v/v to about 95% v/v. The present inventors have found that a contact medium, i.e. an aqueous

25 medium, comprising water and ethanol in a volume ratio of from about 1:50 to about 1:1 is suitable, preferably the ratio is from about 1:10 to about 1:1 such as, e.g. 1:2 or 1:3. Such an aqueous medium may only contain water and ethanol or it may contain other solvents as well.

- 30 The contact is generally carried out without any external heating, but of course heating may be employed to speed up the process. The contact performed may result in a formation of a conjugate, an adduct or a salt or a partial salt but investigations are ongoing in order to clarify this specific question. Without being limited in any way, it is presently believed that the conjugate or adduct formed may be in the form of a salt or

complex formed by a reaction between the therapeutically and/or prophylactically active substance and the alkaline substance employed in process step i) above.

If the active drug substance and the alkaline substance is processed under conditions
5 where an aqueous contact between the two components does not take place (i.e. under anhydrous conditions) then the present inventors have found that the resulting composition does not fulfil the requirements herein with respect to the release the active drug substance from the composition.

10 The mean particle size of the antacid-like substance employed in compositions according to the invention (as raw material) is normally at the most about 250 μm , such as at the most about 225 μm , at the most about 200 μm , at the most about 175 μm , at the most about 150 μm , at the most about 145 μm , at the most about 140 μm , at the most about 135 μm , at the most about 130 μm such as, e.g., in a range of from about 20 μm to about
15 250 μm , in a range of from about 40 μm to about 200 μm , in a range of from about 60 μm to about 175 μm , in a range from about 80 μm to about 150 μm or in a range of from about 100 μm to about 120 μm .

Besides the employment of an alkaline substance in order to enable a suitable contact
20 with the active drug substance, another important ingredient in a composition according to the invention is an ingredient which imparts the necessary mechanical strength to the composition to enable normal handling and, optionally, conventional coating of the composition. In the present context, such an ingredient is denoted "a filler having binding properties". As demonstrated in the Examples herein compositions without such an
25 ingredient or compositions including such an ingredient but having an inappropriate particle size seem to be compositions which are too soft, i.e. have such a poor mechanical strength (friability and crushing strength) that they will not withstand the handling tablets normally have to withstand in order to be used by patients.

30 Examples of a suitable filler having binding properties for use in compositions according to the invention is, e.g., lactose (such as, e.g., Tabletose®, Pharmatose®), sugar derivatives (such as, e.g., mannitol, sorbitol), calcium carbonate (CaCO_3), tricalcium phosphate ($\text{Ca}_5(\text{PO}_4)_3\text{OH}$), calcium hydrogen phosphate (CaHPO_4) (such as, e.g., Di-Cafos®, Di-Tab®, Emcompress® or Pharmacompress®), or the like and/or mixtures thereof.

In the experimental section herein calcium hydrogen phosphate has been employed as an example of a filler having binding properties and the results show that the mechanical strength of the tablets prepared is dependant on the particle size of the calcium hydrogen phosphate employed. Too small or too large a particle size will result in tablets which are
5 too soft to withstand normal handling by patients.

Accordingly, the filler having binding properties as raw material has normally a mean particle size of at the most about 140 μm , such as, e.g., at the most about 130 μm , at the most about 120 μm , at the most about 110 μm , at the most about 100 μm , at the most
10 about 90 μm , at the most about 80 μm , at the most about 70 μm , at the most about 60 μm , at the most about 50 μm , at the most about 40 μm , at the most about 35 μm , at the most about 30 μm or at the most about 25 μm such as, e.g., in a range of from about 10 μm to about 80 μm . or in a range of from about 10 to about 65 μm such as e.g. 15-55 μm .

15 In accordance with the discussion above relating to the particle size, the process step ii) above in a process for the preparation of a composition according to the invention is performed in a conventional high shear mixer employing an energy input which is sufficient to enable a contact to take place between the therapeutically and/or prophylactically active substance and the alkaline substance employed in step i) but at the
20 same time is sufficiently low to avoid formation of a large amount of agglomerates during the mixing.

Thus, in a composition according to the invention, the mean particle size of the particles of the particulate mixture obtained after contact between the active drug substance and the
25 alkaline substance (including any other ingredients present such as, e.g. a filler having binding properties) is at the most about 100% larger than the mean particle size of the powder mixture before the reaction in an aqueous medium. More specifically, the mean particle size of the particle of the particulate composition is at the most 90% such as, e.g., about 80%, about 75%, about 70%, about 65%, about 60%, about 55% or about 50%
30 larger than the mean particle size of the powder mixture before the reaction in an aqueous medium.

The particle size of the particulate mixture is also expressed by means of results obtained from a sieve analysis, namely that at least about 50% w/w such as, e.g., at least about
35 55% w/w. at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at

least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w or at least about 95% w/w of the particles passes through sieve 180 μm . Before the contact with the aqueous medium, the particle size of the powder is also expressed by means of results obtained from a sieve analysis, namely that at least about 90% w/w such as, e.g. at least about 92% w/w, at least about 94% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 97% w/w, at least about 98% w/w or at least about 99% w/w of the particles passes through sieve 180 μm .

With respect to the mean particle size of the particles of the particulate composition obtained after contact of between the active drug substance with the alkaline substance (including any other ingredients present such as, e.g. a filler having binding properties) it is at the most about 250 μm , such as, e.g. at the most about 240 μm , at the most about 230 μm , at the most about 220 μm , at the most about 210 μm , at the most about 200 μm , at the most about 190 μm , at the most about 180 μm , at the most about 175 μm , at the most about 150 μm , at the most about 125 μm , at the most about 100 μm , at the most about 90 μm , at the most about 80 μm or at the most about 75 μm , whenever appropriate, after a reaction in an aqueous medium.

As mentioned above, a composition according to the invention has such a mechanical strength that it can be subjected to normal handling and coating in conventional coating apparatus without breakage or otherwise rupture. Therefore, a composition according to the invention in the form of tablets having a diameter of 9.5 mm—when subjected to a crushing strength test in accordance with Ph. Eur. - has a crushing strength of at least about 50 N such as, e.g., at least about 60 N, at least about 70 N, at least about 80 N such as, e.g., in a range from about 60 to about 130 N, in a range from about 70 to about 120 N or in a range of from about 75 to about 110 N such as from about 80 to about 100 N. With respect to tablets having other diameters than 9.5 mm, a person skilled in the art will know which crushing strength values become relevant.

An important ingredient with respect to imparting the desired mechanical strength to a composition according to the invention (if the composition is in the form of a tablet) is as mentioned above the filler having binding properties. Therefore, a composition according to the invention - when tested as a composition without the filler having binding properties in the crushing strength apparatus according to Ph. Eur. - is contemplated to have a

crushing strength of less than about 45 N such as, e.g., less than about 30 N, less than about 25 N, less than about 20 N, less than about 15 N or less than about 10 N.

In order i) to avoid any substantial degradation of the active drug substance employed in a composition according to the invention and ii) to enable a substantially constant release rate of the active drug substance from a composition according to the invention in the life span of the composition, water content in the composition is at the most about 5% w/w such as, e.g., at the most about 4% w/w, at the most about 3%, at the most about 2% w/w, at the most about 1.5% w/w, at the most about 1.3% w/w, at the most about 1.1% w/w, at the most about 1.0% w/w or at the most about 0.9% w/w determined by a LOD (loss on drying) method (IR dryer, 30 min at 70 °C).

Definitions of selected terms used herein

The term "modified release composition" used in the present context is defined as a composition from which the release of the drug differs from that of a traditional composition. The release rate is in other words controlled and it is possible to manipulate the release rate by e.g. changing the formulation parameters. The term "modified" is often used in the sense of prolonged, but the term is not restricted to an extended or prolonged effect; the term "modified" may as well cover the situation where the release rate is manipulated in such a manner that a quicker release than normally expected is obtained. Thus, in the present context the terms "quick", "fast" and "enhanced" release as well as "controlled", "delayed", "sustained", prolonged, "extended" and other synonyms well known to a person skilled in the art are covered by the term "modified", but with respect to the present invention, the term "modified release" is to be understood as a "quick release", "fast release" or "enhanced release".

The term modified release in the present context refers to a composition which can be coated or uncoated and prepared by using pharmaceutically acceptable excipients and/or specific procedures which separately or together are designed to modify the rate or the place at which the active ingredient or ingredients are released (Ph. Eur. 97).

The terms "quick release", "fast release" or "enhanced release" in the present context refer to a modified release composition of which the release of the active ingredient and its subsequent absorption are fast. More specifically, the terms "quick

release", "fast release" or "enhanced release" mean that for a composition – when subjected to a dissolution method I described herein – at least about 50% w/w of the active substance is dissolved within the first 20 min of the test.

- 5 The term "dosage unit" in the present context refers to one single unit, e.g. a capsule, tablet, a sachet or any other relevant dosage form known within the art. A dosage unit may represent a plurality of individual units which in accordance with the general state of the art may be in the form of a capsule, a tablet, a sachet, etc.
- 10 The term "bioavailability" designates the rate and extent to which the drug is absorbed from the modified release composition.

The terms "NSAIDs" or "NSAID substances" are used herein to designate a group of drugs that belongs to non-steroid anti-inflammatory drug substances and

- 15 pharmaceutically acceptable salts, prodrugs and/or complexes thereof as well as mixtures thereof.

The therapeutic classes mentioned herein are in accordance with the ATC (Anatomical Therapeutic Chemical) classification system.

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Active drug substances

- In the following are given examples of active drug substances which may be incorporated in a composition according to the invention. A majority of the active drug substances
- 25 mentioned are weak acids, i.e. substances which have a pK_a value below about 5.5 such as, e.g., in a range of from about 3.0 to about 5.5 or in a range of from about 4.0 to about 5.0. In this connection it can be mentioned that the pK_a value for lornoxicam is about 4.7, for naproxen about 4.2, for indometacin about 4.5 and for acetylsalicylic acid about 3.5. Moreover, active drug substances like those mentioned above (i.e. weak acids having a
- 30 pK_a value of at the most about 5.5 or about 5.0) generally have a poor solubility in media having a pH below the pK_a value; as an example the solubility of lornoxicam at a pH corresponding to 0.1 N HCl is less than about 1 mg/100 ml at room temperature and active drug substances like acetylsalicylic acid, indometacin and naproxen are regarded as substances which are practically insoluble in water and 0.1 N HCl at room temperature.
- 35 From the discussion relating to solubility and availability of the active drug substance in

order to get access to the circulatory system it should be appreciated that the release (dissolution) of the active drug substance from the composition should be quick under acidic conditions, e.g., in 0.1 N HCl even if the active drug substance has a very low solubility in this medium.

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Relevant examples of active drug substances suitable for use in compositions according to the invention are in general weakly acidic substances such as, e.g., paracetamol and/or NSAID substances like

- 10 - aminoarylcarboxylic acid derivatives like e. g. enfenamic acid, flufenamic acid, isonixin, meclofenamic acid, mefenamic acid, morniflumate, niflumic acid, and tolafenamic acid,
- arylacetic acid derivatives like e.g. aceclofenac, acemetacin, amfenac, bromfenac, cimmetacin, diclofenac, etodolac, fentiazac, glucametacin, indomethacin, lonazolac,
- 15 metiavinic acid, oxametacine, pirazolac, proglumetacin, sulindac, tiaramide, tolmetin, and zomepirac,
- arylcarboxylic acids like e.g. ketorolac and tinoridine,
- arylpropionic acid derivatives like e. g. alminoprofen, bermoprofen, carprofen, dexibuprofen, fenbufen, fenoprofen, flunoxaprofen, flurbiprofen, ibuprofen,
- 20 ibuproxam, ketoprofen, loxoprofen, naproxen, oxaprozin, pranoprofen, protizinic acid, and tiaprofenic acid,
- pyrazoles like e.g. epirizole,
- pyrazolones like e.g. benzpiperylon, mofebutazone, oxyphenbutazone, phenylbutazone, and ramifenazone,
- 25 - salicylic acid derivatives like e.g. acetaminosalol, acetylsalicylic acid, benorylate, eterisalate, fendosal, imidazole salicylate, lysine acetylsalicylate, morpholine salicylate, parsalmide, salamidacetic acid and salsalate,
- thiazinecarboxamides like a.o. ampiroxicam, droxicam, lornoxicam, meloxicam, piroxicam, and tenoxicam,
- 30 - others like bucillamine, bucolome, bumadizon, diferenpiramide, ditazol, emorfazone, nabumetone, nimesulide, proquazone and piroxicam (e.g. in the form of a betacyclodextrin complex).

From a market point especially the following NSAIDs are interesting: lornoxicam,

35 diclofenac, nimesulide, ibuprofen, piroxicam, piroxicam (betacyclodextrin), naproxen,

ketoprofen, tenoxicam, aceclofenac, indometacin, nabumetone, acetmetacin, morniflumate, meloxicam, flurbiprofen, tiaprofenic acid, proglumetacin, mefenamic acid, fenbufen, etodolac, tolfenamic acid, sulindac, phenylbutazone, fenoprofen, tolmetin, acetylsalicylic acid, dexibuprofen and pharmaceutically acceptable salts, complexes
 5 and/or prodrugs and mixtures thereof.

Other relevant active drug substances are COX-2 (COX is an abbreviation for cyclooxygenase) inhibitors like e.g. celecoxib and flosulide.

10 At present, the most preferred drug substance is lornoxicam and pharmaceutically acceptable salts, complexes and prodrugs thereof. Lornoxicam may be present in a composition according to the invention as the sole drug substance or in combination with other drug substances.

15 In those cases where a quick release composition of the present invention includes an NSAID substance as the therapeutically active ingredient, the amount of the active drug substance corresponds to from 1 to about 1600 mg of by weight. Alternatively, the dosage form may contain molar equivalent amounts of pharmaceutically acceptable salts thereof. The dosage form contains an appropriate amount to provide a substantially equivalent
 20 therapeutic effect.

The active substances mentioned above may be present in a composition according to the invention as i) the only drug substance, or ii) together with at least one other active drug substance such as, e.g. an NSAID substance.

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Relevant substances in this context are e.g. antidepressants, opioids, prostaglandine analogs (e.g. misoprostol), glucocorticosteroids, cytostatics (e.g. methotrexate), H₂ receptor antagonists (e.g. cimetidine, ranitidine), proton pump inhibitors (e.g. pantoprazole, omeprazole, lansoprazole), antacids, furosemid, acetaminophen

30 (paracetamol), penicillamine, sulfasalazine and/or auranofin, and – whenever relevant – pharmaceutically acceptable salts, complexes and/or prodrugs and mixtures thereof.

The term “antidepressant” used in the present context includes tricyclic antidepressants as well as other antidepressants and mixtures thereof. Pharmaceutically acceptable salts
 35 and/or complexes of antidepressant are also within the definition of antidepressant. Thus,

the term "antidepressant" is used here to designate a group of drugs that have, to varying degrees, antidepressive properties and/or suitable properties with respect to alleviation or treatment of neurogenic pain and/or phantom pain. In the present context the term "antidepressant" encompasses drug substances mainly from the therapeutic class N06 or

5 from the following drug classification: Psychoanaleptics excluding anti-obesity preparations; anti-depressants/thymoanaleptics including substances used in the treatment of endogenous and exogenous depression such as, e.g., imipramine, nortriptyline, amitriptyline, oxipramol and MAO-inhibiting substances; lithium; combinations of drugs with ataractics; psychostimulants including drugs which increase

10 the psychic and physical performance and which have a fatigue depressing, stimulating effect such as, e.g., fentyllines, fencamfamine, methylphenidate, amphetamines; psycholeptic-psychoanaleptic combinations; nootropics [which are a class of psychoactive drugs which are claimed to have a selective action on integrative functions of the CNS. Their action is alleged to be particularly associated with intellectual function, learning and

15 memory. Nootropics include preparations containing substances such as piracetam, pyritinol, pyrisuccideanol maleate, meclofenoxate, cyprodenate and their combinations with other substances, excluding those products with a vasodilatory action (see the therapeutic class C04A). Combinations with cardiac glycosides are classified in the therapeutic class C01A]; and neurotonics and other miscellaneous products including

20 products which are not classified above such as single or combination products containing bisibutiamin, deanol and derivatives, GABA, GABOB, N-acetyl asparaginic acid glutaminic acid and salts, kavain, phospholipid, succinodinitrate.

The presently most interesting drug substances belong to the tricyclic antidepressants.

25 Relevant examples of antidepressants are: tricyclic antidepressants such as, e.g. dibenzazepine derivatives like carpipramine, clomipramine, desipramine, imipramine, imipraminoxide, imipramine pamoate, lofepramine, metapramine, opipramol, quinupramine, trimipramine; dibenzocycloheptene derivatives like amitriptyline, amitriptyline and chlordiazepoxide, amitriptyline and medazepam, amitriptyline and

30 pridinol, amitriptyline and perphenazine, amitriptylinoxide, butriptyline, cyclobenzaprine, demexiptiline, nortriptyline, nortriptyline and diazepam, nortriptyline and perphenazine, nortriptyline and fluphenazine, nortriptyline and flupentixol, noxiptilin, protriptyline; dibenzoxepine derivatives like doxepin; and other tricyclic anti-depressants like

35 adinazolam, amoxapine, dibenzepin, dimetacrine, dosulepin, dosulepin and diazepam, dothiepin, fluacizine (fluoracyzine, toracizin), iprindole, maprotiline, melitracen,

melitracene and flupentixol, pizotiline, propizepine, and tianeptine; other antidepressants like 5-hydroxytryptophan, ademetonine, amfebutamone, amfebutamone hydrochloride, amineptine, amineptine hydrochloride, amisulpride, fluoxetine hydrochloride, fluoxetine, hypericin, lithium carbonate, sertraline hydrochloride, sertraline, St John's wort dry extract,

5 trimipramine maleate, citalopram, citalopram hydrobromide, clomipramine chloride, clomipramine hydrochloride, d-phenylalanine, demexiptiline, demexiptiline hydrochloride, dimethacrine tartrate, dothiepin, dothiepin hydrochloride, doxepin, fluphenazine hydrochloride, fluvoxamine, fluvoxamine hydrogen maleate, fluvoxamine maleate, ginkgo biloba, indalpine, isocarboxazide, johanniskrauttrockenestragt, 1-tryptophan, lithium

10 citrate, lithium sulfate, lofepramine, maprotiline, maprotiline hydrochloride, maprotiline mesilate, medifoxamine, metaprimine fumarate, mianserin, moclobemide, nitroxazepine hydrochloride, nomifensine, nomifensine maleate, nomifensin hydrogenmaleat, oxitriptan, paroxetine, paroxetine hydrochloride, phenelzine, phenelzine sulfate, piracetam, pirlindole, pivagabine, prolintane hydrochloride, propizepine hydrochloride, protriptyline

15 hydrochloride, quinupramine, remoxipride hydrochloride, rubidium chloride, setiptiline maleate, tianeptine sodium, trazodone hydrochloride, venlafaxine hydrochloride, maprotiline, toloxatone, tranlycypromine, trazodone, trazodone hydrochloride, viloxazine, viloxazine hydrochloride, zimelidine, zimelidine dihydrochloride.

20 At present, the most interesting antidepressant drug substances for use in a composition according to the invention are amitriptyline and/or imipramine and pharmaceutically acceptable salts, complexes and prodrugs thereof. Amitriptyline and/or imipramine may be present in a composition according to the present invention either as the sole drug substance or in combination with other drug substances. Amitriptyline is a very interesting

25 drug candidate with respect to preventing and/or treating neurogenic pains and phantom pains.

The term "opioid" is used here to designate a group of drugs that are, to varying degrees, opium- or morphine-like in their properties. The term includes natural and synthetic

30 opioids as well as active metabolites such as morphine-6-glucuronide and morphine-3-glucuronide, and mixtures of opioids. Pharmaceutically acceptable salts and/or complexes of opioids are also within the definition of opioids.

Further relevant examples of opioids for use in compositions according to the invention

35 include alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide,

buprenorphine butorphanol, clonitazene, codeine, cyclazocine, desomorphine, dextromoramide, dezocine, diampromide, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene fentanyl, 5 heroin, hydrocondone, hydromorphone, hydroxypethidine, isomethadone, dextropropoxyphene, ketobemidone, levallorphan, levorphanol, levophenacymorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, nalbuphine, narceine, nicormorphine, norlevorphanol, normethadone, nalorphine, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, 10 pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propiram, propoxyphene, sufentanil, tilidine, tramadol, salts thereof, mixtures of any of the foregoing, mixed μ -agonists/antagonists, μ - and/or κ -agonists, combinations of the above, and the like.

15 Within the scope of the invention is of course that more than one active drug substance may be present in a composition, e.g. more than one NSAID substance and/or drug substances within the same or different therapeutic classes. Specific relevant therapeutic classes are M01A (NSAIDs), R05D, N02 (analgesics), N2A (opioids) and N2B (non-narcotic analgesics).

20

Dosage

In general, the dosage of the active drug substance present in a composition according to the invention depends *inter alia* on the specific drug substance, the age and condition of 25 the patient and of the disease to be treated.

Compositions according to the invention will generally contain an amount of the active drug substance which enables a sufficient therapeutic and/or prophylactic response.

30 In order to illustrate the broad ranges of suitable doses, the recommended daily doses for selected NSAID substances is listed in the following:

Aceclofenac: 200 mg

Diclofenac: 100 mg

35 Etodolac: 400 mg

- Fenbufen: 900 mg
- Fenoprofen: 1.5 g
- Flurbiprofen: 200 mg
- Ibuprofen: 1.6 g
- 5 Indometacin: 100 mg
- Ketoprofen: 200 mg
- Meloxicam: 15 mg
- Nabumeton: 1 g
- Naproxen: 750 mg
- 10 Piroxicam: 20 mg
- Sulindac: 300 mg
- Tenoxicam: 20 mg
- Tiaprofenic acid: 600 mg
- Tolfenamic acid: 400 mg
- 15 Tolmetin: 800 mg

The amount of e.g. an NSAID substance in a quick release composition according to the invention may be selected so that it corresponds to about 1 mg, 2 mg, 3 mg, 4 mg, 5 mg, 8 mg, 10 mg, 12 mg, 16 mg, 20 mg, 24 mg, 25 mg, 30 mg, 32 mg, 50 mg, 60 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, 1 g, 1.1 g, 1.2 g, 1.3 g or 1.6 g of NSAID substance which are dosages generally known in the art.

A composition according to the invention may be produced in different series of dosage forms of e.g. 4 mg, 8 mg, 12 mg, 16 mg, 24 mg, 32 mg etc., each of the series having individual properties resulting from the design of modified release of the composition. Any desired total dosage can then be selected from the relevant dosage forms within each of the series.

The preferred dosage form according to the invention is in the form of a capsule, tablet, sachet etc. The size of the dosage form is adapted to the amount of the active drug substance contained in the composition.

The above suggested dosage amounts should not be regarded as a limitation of the scope of the invention as it is obvious for the skilled person that any desired amount of the

active drug substance may be applied and is only limited by the size of the composition and the type of the active drug substance.

Pharmaceutically acceptable excipients

5

Apart from the active drug substance in the composition, a pharmaceutical composition according to the invention may further comprise pharmaceutically acceptable excipients.

In the present context, the term "pharmaceutically acceptable excipient" is intended to
10 denote any material which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect *per se*. A pharmaceutically acceptable excipient may be added to the active drug substance with the purpose of making it possible to obtain a pharmaceutical formulation which has acceptable technical properties. Although a pharmaceutically acceptable excipient may have some influence on the release of the
15 active drug substance, materials useful for obtaining modified release are not included in this definition.

Fillers/diluents/binders may be incorporated such as sucrose, sorbitol, mannitol, lactose (e.g., spray-dried lactose, α -lactose, β -lactose, Tabletose®, various grades of Pharma-
20 tose®, Microtose or Fast-Floc®), microcrystalline cellulose (e.g., various grades of Avicel®, such as Avicel® PH101, Avicel® PH102 or Avicel® PH105, Elcema® P100, Emcocel®, Vivacel®, Ming Tai® and Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low-substituted) (e.g. L-HPC-CH31, L-HPC-LH11, LH 22, LH 21, LH 20, LH 32, LH 31, LH30), dextrans, maltodextrins (e.g. Lodex® 5 and Lodex® 10),
25 starches or modified starches (including potato starch, maize starch and rice starch), sodium chloride, sodium phosphate, calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate), calcium sulfate, calcium carbonate. In pharmaceutical formulations according to the present invention, especially microcrystalline cellulose, L-hydroxypropylcellulose, dextrans, maltodextrins, starches and modified starches have
30 proved to be well suited.

Disintegrants may be used such as cellulose derivatives, including microcrystalline cellulose, low-substituted hydroxypropyl cellulose (e.g. LH 22, LH 21, LH 20, LH 32, LH 31, LH30); starches, including potato starch; croscarmellose sodium (i.e. cross-linked
35 carboxymethylcellulose sodium salt; e.g. Ac-Di-Sol®); alginic acid or alginates; insoluble

polyvinylpyrrolidone (e.g. Polyvidon® CL, Polyvidon® CL-M, Kollidon® CL, Polyplasdone® XL, Polyplasdone® XL-10); sodium carboxymethyl starch (e.g. Primogel® and Explotab®).

- 5 Glidants and lubricants may be incorporated such as stearic acid, metallic stearates, talc, waxes and glycerides with high melting temperatures, colloidal silica, sodium stearyl fumarate, polyethylenglycols and alkyl sulphates.

- Surfactants may be employed such as non-ionic (e.g., polysorbate 20, polysorbate 21,
10 polysorbate 40, polysorbate 60, polysorbate 61, polysorbate 65, polysorbate 80, polysorbate 81, polysorbate 85, polysorbate 120, sorbitane monoisostearate, sorbitanmonolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan monooleate, sorbitan sesquioleate, sorbitan trioleate, glyceryl monooleate and polyvinylalcohol), anionic (e.g., docusate sodium and sodium lauryl sulphate) and cationic
15 (e.g., benzalkonium chloride, benzethonium chloride and cetrimide) or mixtures thereof.

Other appropriate pharmaceutically acceptable excipients may include colorants, flavouring agents, and buffering agents.

- 20 A coating may also be applied on a composition according to the invention provided that the coating does not substantially retard the release of the active drug substance from the composition. Typically, a film coating may be employed.

Manufacturing processes

25

As discussed above, the invention also relates to a method for preparing a composition according to the invention. The method comprising the steps of

- i) mixing the therapeutically and/or prophylactically active substance with a) an
30 alkaline substance, b) a filler having binding properties, and, optionally, c) other pharmaceutically acceptable excipients to obtain a powder mixture,
- ii) contacting the thus obtained powder mixture with an aqueous medium to obtain a
wet powder,

35

- iii) drying the thus obtained wet powder at a temperature above room temperature until the water content in the powder is at the most about 5% w/w determined as described herein, to obtain a first particulate mixture,
 - 5 iv) sieving the thus obtained first particulate mixture,
 - v) optionally, adding any further pharmaceutically acceptable excipients to obtain a second particulate mixture,
 - 10 vi) optionally, compressing the thus obtained second particulate mixture into tablets, and
 - vii) optionally, coating the thus obtained tablets.
- 15 The individual steps of the method are performed in apparatus which are suitable for the specific type of process step. It is of course advantageous to performed more than one step in the same apparatus provided that the critical conditions can be controlled in the desired manner.
- 20 With respect to step i), the most critical parameter is the particle size of the starting material, cf. the discussion above, especially the particle size of the filler having binding properties.

Step ii) is a very important step and the conditions under which this step is carried out are very critical. Most important is it that in this step the powder is subjected to not a granulation process but a wetting process resulting in a particulate material in which the individual particles of the powder mixture are brought into contact and held together by binding forces which are established by the energy input given during step ii) The present inventors have made investigations which show that A) if a normal granulation process is employed, i.e. a process which results in the formation of agglomerates, or B) if a direct compression (see Example 20b) procedure is employed, i.e. a process in which step ii) is irrelevant because no wetting of the powder blend takes place, then the final composition does not fulfil the requirements with respect to quick release. However, as reported in the experimental section herein the use of the correct conditions may lead to a composition

from which almost 100% w/w of the active substance (at least 90-95% w/w) is released *in vitro* within the first 10 min of the test employing Dissolution method I as described below.

The mechanism which is believed to take place in step ii) is to bring the active substance
5 and the alkaline substance in close contact and at the same time utilise conditions which
are favourable with respect to building up a composition which has optimal disintegration
and dissolution properties. To this end, it is believed that employment of an alkaline
substance which is able to produce gas, carbon dioxide, upon contact with water (or an
aqueous medium having a pH below 7) is acceptable as a certain production of gas
10 during the wetting procedure facilitates the necessary controlled disintegration of the final
composition, i.e. avoiding a too fast disintegration due to an excessive amount of gas
production when the final composition disintegrates. To this end, the inventors have
performed experiments in which the active substance and the alkaline substance have
been subjected to a treatment with an aqueous medium and subsequently dried and then
15 the particulate material obtained in this manner has been employed in step i) of the
method described above. However, this procedure does not lead to a satisfactory result
and the composition obtained has a unacceptable shelf-life, i.e. the aqueous pre-
treatment of the active substance with the alkaline substance seems to have a negative
influence on the chemical stability of the active substance itself.

20

The critical parameters in step ii) are the contact medium, the contact time and the energy
input (i.e. the energy added to the powder mixture to build up the particulate material).
The particle size of the resulting particulate material is a very important parameter, cf. the
discussion above, but as mentioned above it is possible successfully to obtain suitable
25 composition even if the particle size of the particulate material is larger than the sizes
claimed if the particles either are soft or have an increased porosity.

The contact medium is not used as a granulation medium, e.g. no water-soluble binders is
present in the medium. Typically the medium is an aqueous medium having a composition
30 as described hereinbefore. A preferred medium is a medium containing ethanol and water
and wherein the concentration of ethanol in the solvent is from about 0% v/v to about 95%
v/v such as, e.g., from about 10% v/v to about 90% v/v, from about 10% v/v to about 80%
v/v, from about 15% v/v to about 70% v/v, from about 15% v/v to about 60% v/v, from
about 20% v/v to about 50% v/v, from about 20% v/v to about 40% v/v, from about 25%
35 v/v to about 35% v/v such as, e.g. about 33.3% v/v. An especially suitable aqueous

medium is a medium containing ethanol and water in a volume ratio of from about 1:10 to about 1:1 such as from about 1:3 to about 1:1.5, e.g. 1:2.

With respect to the energy supply during step ii) the present inventors have found that the
5 use of a mixer of the type high speed impeller is suitable.

The energy supplied during step ii) may advantageously be added discontinuous, i.e. with intervals of wet-massing and wet-resting (i.e. intervals in which the aqueous medium is added to the powder during mixing and intervals in which no adding of aqueous medium
10 takes place and no mixing takes place as exemplified in Example 16).

As a starting point of determining the necessary energy supply when either changing the batch size or the apparatus, the swept volume is a guidance.

15 The swept volume is related to the energy input and is defined in the following way:

The vertical swept volume out by one impeller blade at each revolution is calculated by dividing the blade area into vertical segments. Based on this volume and the impeller speed, the volume swept out by the blades per second is determined relative to the
20 volume of the product or the volume of the bowl.

Moreover, it is important that step ii) is performed in a suitable apparatus which enables an energy input which a) is sufficient to bringing the particles in contact with the aqueous medium without substantially deteriorate the stability of the final composition and/or b) is
25 sufficient to bringing the therapeutically and/or prophylactically active substance and the alkaline substance in contact with the aqueous medium without negatively influencing the release rate of the active substance from the final composition.

As discussed above, step ii) is typically performed in a conventional high shear mixer
30 employing an energy input which is sufficient to enable a contact to take place between the therapeutically and/or prophylactically active substance and the alkaline substance employed in step i) but at the same time is sufficiently low to avoid formation of a large amount of agglomerates during the mixing.

The mean particle size of the particles of the first particulate mixture is at the most about 100% larger than the mean particle size of the powder mixture from step i) before subjecting the powder mixture to the reaction in the aqueous medium employed in step ii).

- 5 More specifically, the mean particle size of the particle of the first particulate mixture is at the most 90% such as, e.g., about 80%, about 75%, about 70%, about 65%, about 60%, about 55% or about 50% larger than the mean particle size of the powder mixture from step i) before subjecting the powder mixture to the reaction in an aqueous medium employed in step ii).

10

The particle size is also expressed by results of a sieve analysis and then the following sizes are relevant:

- The powder obtained in step i) has such a particle size that - when the powder is
- 15 subjected to a sieve analysis - then at least about 90% w/w such as, e.g. at least about 92% w/w, at least about 94% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 97% w/w, at least about 98% w/w or at least about 99% w/w of the particles passes through sieve 180 μm , and the first particulate mixture obtained in step iii) has such a particle size that - when the particulate composition is
- 20 subjected to a sieve analysis - then at least about 50% w/w such as, e.g., at least about 55% w/w, at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w or at least about 95% w/w of the particles passes through sieve 180 μm .
- 25 Typically, the mean particle size of the particles of the first particulate mixture is at the most about 250 μm , such as, e.g. at the most about 240 μm , at the most about 230 μm , at the most about 220 μm , at the most about 210 μm , at the most about 200 μm , at the most about 190 μm , at the most about 180 μm , at the most about 175 μm , at the most about 150 μm , at the most about 125 μm , at the most about 100 μm , at the most about 90 μm ,
- 30 at the most about 80 μm or at the most about 75 μm .

- Step iii) in which the wet particulate material is dried is of course also important in order to obtain a proper shelf-life of the product. The remaining steps are steps well known in the art of pharmaceutical formulation and a person skilled in the art knows hand-books in
- 35 which further details are found.

In the following examples, the invention is further disclosed.

MATERIALS AND METHODS

5

Materials employed in the compositions which were investigated in the course of development of the present invention were as given in the following. In those cases where reference is given to an official pharmacopoeia, the reference is to the current edition of the stated pharmacopoeia.

10

The following abbreviations are used:

Ph. Eur.: European Pharmacopoeia

USP/NF: United States Pharmacopoeia National Formulary

DLS: Dansk Lægemiddelstandard

15

Materials	Quality	Manufacturer
Cellulosum microcrystallinum (Avicel PH 101)	Ph.Eur.	FMC
20 Dibasic Calcium Phosphate, Anhydrous (Calcium hydrogen phosphate)	USPNF	Kyowa
Sodium bicarbonate	USPNF	Kirsch
Hydroxypropylcellulose (HPC L fine)	Ph. Eur.	Nippon Soda
Low-substituted Hydroxy Propyl Cellulose	USPNF	Shin-Etsu
25 Calcium stearate	Ph.Eur.	Akcros Chemicals
Ethanol, 96 %	DLS	Danisco
Aqua Purificata	Ph. Eur.	
Macrogol 6000 (polyethylene glycol)	Ph. Eur.	BASF
30 Hydroxypropylmethylcellulose (Pharmacoat 603)	USP	Shin-Etsu
Hydroxypropylmethylcellulose (Pharmacoat 606W)	USP	Shin-Etsu
Magnesium stearate	Ph. Eur.	Akcros
35 Polypylasdone XL	USPNF	ISP

	Aerosil 200	Ph. Eur.	Degussa
	Talc	Ph. Eur.	Luzenac val chisone
	Titanium dioxide	Ph. Eur.	Bayer
	Hydroxypropylmethylcellulose 5	Ph. Eur.	Dow
5	Propylene glycol	Ph. Eur.	Arcochemie
	Ibuprofen	Ph. Eur.	Albemarle S.A.
	Furosemide	Ph. Eur.	Assia Chemical Industries Ltd.
	Sodium lauryl sulfate		Henkel
10	Lornoxicam		Nycomed

DISSOLUTION METHOD I

0.07 N HCl (lornoxicam)

- 15 Lornoxicam has a very low solubility under acidic conditions such as in 0.1 or 0.07 N HCl. *Inter alia* in order to show that the relatively fast release fraction indeed releases lornoxicam at acidic pH (simulating the pH conditions in the stomach), dissolution method I is employed.

20 Test method

- Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7 and Perkin Elmer UV/VIS Spectrometer Lambda 2. The measurement was performed continuously using Perkin-Elmer Dissolution Software
- 25 for Lambda Series UV/VIS Spectrometers Version 3.0/ JAN 94. The calculations were performed using the same software.

Glass fibre filter: Whatman GF/F

- 30 Dissolution medium: 900.0 ml dissolution medium (see below)

Number of revolutions: 100 rpm

Stirrer: Paddle

35

Temperature of dissolution medium: 37°C ± 0.5°C

Measuring times: every 5 minutes and 20 min after the start of the test (details appear from the following examples)

5 Analysis method

Detection wavelength: $\lambda = 378 \text{ nm}$

Measuring equipment: UV/VIS – spectrophotometer, 1 cm cuvette

10

Preparation of reagents

Dissolution medium: Weigh out 50.0 g of sodium chloride and measure out 141.6 ml of concentrated hydrochloric acid. Dissolve the chemicals in distilled water and dilute to 25 l
15 with distilled water.

Standards

Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 200 $\mu\text{g/ml}$
20 lornoxicam were prepared. Lornoxicam is dissolved in solvent for standards (cf. below).

Standards: 20.00 ml of each of the stock solutions is added to the reference vessel (cf. below).

25 Solvent for standards: 1.5 % w/w aqueous sodium acetate solution : methanol (1:1)

Test procedure

900 ml of dissolution medium is filled to each of the vessels (typically three or six vessels
30 for the product and one vessel for reference solution). The medium is heated to $37^\circ\text{C} \pm 0.5^\circ\text{C}$. The product to be tested (e.g. a therapeutically and/or prophylactically active substance, a particulate composition, a granulate, granules or a composition in the form of a tablet, capsule or a sachet) is placed in the vessel. In the last vessel, 20.0 ml of each of the stock solutions are added. The spindle is started, and the absorbance of the

samples and standards is measured at 378 nm with zero setting towards the dissolution medium.

The percentage dissolved is measured over a suitable time interval.

5

Calculation for dissolution method

Percentage dissolved was calculated with reference to an external standard in the reference vessel.

10

The concentration of the standard in the reference vessel is calculated by the formula below:

$$15 \quad \text{mg lornoxicam per 1000 ml} = \left(\frac{q_1 \cdot 20}{V} + \frac{q_2 \cdot 20}{V} \right) \cdot \frac{1000}{940}$$

Where:

- q_1 = amount of standard weighed out for S_1 (mg)
- 20 q_2 = amount of standard weighed out for S_2 (mg)
- 20 = added volume of S_1 and S_2 to the reference vessel (ml)
- V = dilution volume of the standard (ml)
- 940 = volume in the reference vessel after addition of the standards (S_1 and S_2) to the vessel (ml)
- 25 1000 = conversion factor to 1000 ml

The content of lornoxicam as percentage dissolved was calculated from the formula below:

30

$$\frac{\text{abs}_{\text{sample}} \cdot \text{StA} \cdot 900 \cdot x \cdot 100}{\text{abs}_{\text{StA}} \cdot 1000 \cdot q_{\text{tablet}} \cdot 8} \cdot \frac{n}{100}$$

35 Where

- $\text{abs}_{\text{sample}}$ = absorbance measured in each vessel containing samples
- StA = mg lornoxicam pr 1000 ml in the vessel containing standard
- 900 = volume of the medium (ml)

100	=	factor converting to percent
abs_{STA}	=	absorbance measured in vessel containing the standard
1000	=	factor converting the concentration of the standard to mg/ml
8	=	declared content (mg) in the tablet
5 n	=	potency of the standard (%)
100	=	factor converting to percent

Determination of dissolution rate – solubility method I

- 10 The dissolution rate of an active substance is determined using the same procedure as described under "Dissolution method I" above and with any relevant modification in the calculation method described.

Test for resistance to crushing of tablets

15

The test is performed in accordance with the guidelines given in Ph.Eur. 1997, pp 135-136.

- The following examples are intended to illustrate specific embodiments of the present
20 inventions but are not intended in any way to limit the invention.

EXAMPLE 1

- Investigation of the influence of various process parameters on the dissolution rate of**
25 **the final composition**

- Initial investigations by the inventors have indicated that the dissolution rate of a therapeutically and/or prophylactically active substance seems to be dependant on the manufacturing process employed. Especially, it was judged necessary to control critical
30 parameters like e.g. i) spray pressure during the addition of reaction medium, ii) reaction time, iii) amount of reaction medium added and iv) the mixing intensity (i.e. \pm employment of a chopper). Accordingly, labtrials based on a 2^4 factorial design with replication of centre points were performed.

The purpose of the trials was to investigate the influence of certain process parameters on the dissolution of the therapeutically and/or propylactically active substance from the composition obtained. The dissolution test was performed in 0.07 N hydrochloric acid employing the dissolution method I described herein and the amount of active substance released and dissolved after 20 min of the dissolution test was determined.

The factors and the levels investigated are listed below:

Factors	Lower level	High level
Spray pressure ^a	0.5 bar	2.0 bar
Reaction time ^b	2 min	9 min
Amount of medium	1440 g	1640 g
Intensity of mixing (+/- employment of chopper)	-	+ ^c

^a: the spray pressure was measured just before the inlet of air to the nozzle

10 ^b: excl. time for distribution of the water

^c: the speed of the chopper was 1

The design included 20 trials as the centrepoints (with (+) or without (–) chopper) were replicated once. The composition employed throughout the trials is described in the following together with the manufacturing process employed for trial 1 (batch No. 30069733). The manufacturing process for the other trials was in accordance with trial 1 apart from the modifications which were necessary in order to test the above-mentioned process parameters (see Table 1 below).

20	I	Lornoxicam	80.0 g
	II	Sodium hydrogen carbonate	400.0 g
	III	Avicel PH 101	960.0 g
	IV	Calcium hydrogen phosphate anhydrous	1104.0 g
	V	L-HPC	480.0 g
25	VI	Hydroxy propyl cellulose	160.0 g
	VII	Purified water	1230.0 g
	VIII	Ethanol 99,9 %	410.0 g
	IX	Calcium stearate	5.0 g*

* amount adjusted for a total of 1 kg of I-VI.

II-VI were admixed for 6 min in a Fielder intensive mixer with impeller speed I and without
5 use of chopper. Then a 1 kg aliquot was mixed with I in a planetary mixer for 10 min. The mixture was sieved through a 0.5 mm sieve and then admixed in the Fielder to the remaining II-VI mixture.

VII + VIII were mixed and applied to the mixture (I – VI) by a 2 components nozzle with a
10 spray pressure of 0.5 bar and with a spraying time of approx. 2 min. The impeller speed was I and the chopper speed I. When spraying was completed, the mixing was continued for 9 min at impeller speed I and chopper speed I.

The drying of the wet mixture was carried out in a Aeromatic fluid bed with an inlet air
15 temp of 65 °C. The drying was continued for 45 min. Thereafter, the mixture was sieved through a 1.0 mm sieve and the drying process was continued with an inlet air temperature of 80 °C. When the outlet temperature reached 50 °C, after approx. 20 min, the drying was stopped.

20 1200 g of the thus obtained particulate mixture were sieved through a 0.7 mm sieve. IX was sieved through a 0.3 mm sieve and admixed to 1000 g of the sieved particulate mixture in a planetary mixer for 10 min.

The thus obtained particulate mixture was compressed by a Korsch rotary tableting
25 machine. Punches: 9.5 mm. A compound cup was used. Weight of the tablet: 320 mg.

Process parameters employed and dissolution rates obtained from compositions corresponding to trials 1-20 are shown in the following Table 1.

Table 1

2 ⁴ factorial design with replication of centre point						
Batch No.	Trial No.	Pressure (bar)	Time (min)	Amount (g)	Chopper yes/no	Release 20 min %
30069733	1	0.5	9	1640	yes	91.85
1079732	2	2	2	1440	yes	89.88
2079732	3	0.5	9	1640	no	90.85
2079734	4	0.5	2	1440	yes	92.83
3079732	5	1.25	5.5	1540	yes	94.14
7079732	6	2	9	1640	yes	79.64
8079732	7	2	9	1640	no	84.17
8079734	8	2	2	1640	yes	88.14
9079732	9	0.5	9	1440	no	91.24
10079732	10	2	9	1440	yes	93.76
11079732	11	2	9	1440	no	95.8
14079732	12	2	2	1640	no	93.77
1479735	13	2	2	1440	no	89.49
15079732	14	1.25	5.5	1540	no	94.03
15079734	15	1.25	5.5	1540	no	92.07
16079732	16	0.5	2	1440	no	88.99
21079732	17	0.5	9	1440	yes	95.23
21079734	18	0.5	2	1640	no	93.93
22079732	19	1.25	5.5	1540	yes	94.54
22079734	20	0.5	2	1640	yes	94.25

5 In general the following technical properties of the tablets were obtained (uncoated cores):

Water content (LOD – 30 min at 70 °C): 1.4-2.2 %

Disintegration time (mean): 3 - 6 min.

Tablet hardness (crushing strength) (mean): 80 - 100 N

10 Uniformity of the mass (S_{rel}): 1 - 2%

Conclusion

As shown in Table 1 above, the dissolution of lornoxicam from the various compositions tested varies from 79% w/w to about 94% w/w (the amount dissolved has been determined after 20 min of the dissolution test employing dissolution method I described herein).

Statistical analysis showed that the following process parameters were significant or almost significant at the 5% level with respect to influence on the dissolution rate.

10

Spray pressure ($P = 0.03$)

Amount of medium ($P = 0.06$)

Interactions between spray pressure and amount of medium ($P = 0.02$)

Interactions between spray pressure and chopper ($P = 0.03$)

15

Interactions between amount of medium and reaction time ($P = 0.002$)

Interactions between spray pressure, reaction time and amount of medium ($P = 0.04$)

EXAMPLE 2

20 **Design of lornoxicam compositions having a quick release of lornoxicam in 0.07 N hydrochloric acid**

Based on the results obtained in the factorial design described in Example 1 and the aim of approaching or reaching almost a 100% w/w release after 20 min, three realistic estimates of values for the process parameters were calculated. The values of the process parameters are described in Table 2 below. The composition and manufacturing process were identical to trial 1 given in Example 1.

Table 2

Trial (Batch No.)	Nozzle	Spray pressure (bar)	Reaction time (min. *)	Amount of medium (g)	Chopper Yes/No	Release 20 min. (%)	Cellulose, microcryst. (quality)
1 (15089734)	2- component	2.2	16	1440	No	97.63	Ming Tai
2 (15089736)	2- component	0.5	2	1925	No	96.06	Ming Tai
3 (15089738)	2- component	1.6	8.5	1320	Yes	93.87	Ming Tai
4 (26089732)	2- component	2.2	16	1440	No	97.20	FMC

* Excluding the time for distribution of water

- 5 Trials Nos. 1-3 were manufactured with cellulose, microcrystalline supplied from Ming Tai. In order to investigate whether i) the results obtained with respect to the technical properties of the composition and ii) the results obtained with respect to the release of lornoxicam from the composition were influenced by employment of a specific quality of microcrystalline cellulose, another quality from another supplier (FMC) was included in
- 10 trial 4 (batch No. 26089732). Trial 4 was identical to trial 1 in Table 2.

The technical properties of tablets obtained from trials 1-4 were identical to the results obtained in Example 1.

15 Conclusion

As shown in Table 2 a release of 98% w/w was achieved after 20 min, i.e. a significant improvement of the dissolution rates compared with those obtained in Example 1. Thus, the percentages released were approaching 100%.

20

Comparing the results from trial 4 (26089732 FMC) with trial 1 (15089734 Ming Tai) given in Table 2, indicate that no significant difference in release or technical properties of the compositions have been observed.

EXAMPLE 3**Investigation of the influence of the quality of sodium hydrogencarbonate employed**

- 5 The labtrials described in the following were based on the employment of sodium hydrogencarbonate obtained from different suppliers.

Two identical compositions (trials corresponding to batch Nos. 23079733 and 23079735) were manufactured in order to test sodium hydrogencarbonate (mean particle size ~ 120
10 μm) supplied from Kirsch. Previously, sodium hydrogencarbonate (mean particle size ~ 105 μm) supplied from Tosho was used.

The manufacturing process parameters were identical to trial 5 described in Table 1 given in Example 1.

15

Dissolution properties of the cores

About 94% w/w for both trials (percentages dissolved after 20 min employing the dissolution method I described herein).

20

The technical properties were identical to those described in Example 1.

Conclusion

- 25 There is no significant difference between the release results of the 2 trials performed, i.e. the quality of sodium hydrogencarbonate employed does not seem to have any significant influence within the variations tested on the dissolution behaviour of a lornoxicam containing composition. Furthermore, the small variation with respect to mean particle size does not seem to have any important influence on the dissolution behaviour of a
30 composition according to the invention.

EXAMPLE 4**Investigation of a process parameter (application of reaction medium) on the dissolution behaviour**

5

The labtrial described in the following was based on the use of a 1-component nozzle.

In this trial (batch No. 27089732) a 1-component nozzle was used in order to apply the reaction medium. The composition and manufacturing process are identical to trial 1 in

10 Example 1 apart from the following parameters:

Spray pressure: 3.5 bar

Reaction time: 16 min.

Amount of reaction medium: 1440 g

15 No use of chopper.

Dissolution properties of the cores

Release after 20 min was 98.3%.

20

The technical properties of the tablets were identical to those given in Example 1.

Conclusion

25 There is no significant difference in release behaviour compared with trial 4 in Example 2. Accordingly, using a 1-component nozzle in production scale should then be possible.

EXAMPLE 530 **Upscaling to production scale level**

Production scale trial:

One trial (batch No. of the cores: 962620) was scaled up to production scale. The composition and manufacturing process of a batch size of 250,000 tablets are described

35 below:

(Kg/250,000 tablets)

	I	Lornoxicam	2.0 kg
5	II	Sodium hydrogencarbonate	10.0 kg
	III	Cellulose, microcrystalline PH 101	24.0 kg
	IV	Calcium hydrogen phosphate anhydrous	27.6 kg
	V	L-HPC	12.0 kg
	VI	Hydroxy propyl cellulose	4.0 kg
10	VII	Calcium stearate	0.4 kg
	VIII	Purified water	27.0 kg
	IX	Ethanol	9.0 kg
	X	Filmcoat K01187	30.3 kg

- 15 II-VI were admixed in a Diosna intensive mixer with impeller speed I and chopper speed I for 1 min. Then a 10 kg aliquot was taken out of the mixer. 5 kg of this sample was manually mixed with I. A smaller part of the remaining II-VI mixture was sieved in a Quadro Comil U 20 through a 062R sieve. Then, the I-VI mixture was sieved and added to the remaining part of the II-VI mixture followed by admixture in the Diosna to the
- 20 remaining II-VI mixture. The impeller speed was I and the chopper was I for 1 min.

VIII and IX were admixed and applied to the mixture by a 1-components nozzle (Delavan ¼ BNM22X) with a spray pressure of 6.2 bar and with a spraying time of about 3 min. Impeller speed I and chopper speed I. When the spraying was completed, the reaction

25 was continued 13 min at impeller speed I and no chopper was used.

The drying was carried out in an Aeromatic fluid bed with an inlet air temperature of about 65 °C and was continued for 45 min. Then the drying process was continued with an inlet air temperature of about 80°C. When the outlet temperature was about 42°C and RH %

30 (over the mixture) was about 17%, the drying was terminated. The LOD of the thus obtained particulate mixture was determined to be 1.0 %.

The particulate mixture obtained was sieved in a Frewitt through a 0.71 mm sieve. VII was sieved in Quadro Comil U20 through a 062R sieve and admixed to the sieved particulate

35 mixture in Diosna mixer for 25 sec. The impeller speed was I.

The particulate mixture was compressed into tablets by use of a Beta press rotary tableting machine supplied by Manesty. Punches: 9.5 mm. A compound cup was used.

5 Technical properties of uncoated tablets

Humidity (LOD): 1.2-1.4%

Disintegration time: 1'45" - 2 min.

Tablet hardness: 80-100 N.

10

Dissolution properties of the cores

After 20 minutes 99.25% w/w was released (dissolution method I as described herein)

- 15 The cores were coated (batch No. of the coated tablets: 962640) with a white HPMC coat (Filmcoat K01187) in an Accela Cota 150 having 3 nozzles. Spray pressure was 6 bars as measured at the control panel and the liquid flow rate was approx. 175 g/min at the start of the process and approx. 130 g/min at the end of the process. The composition of the coat is described below:

20

I	Methylhydroxypropylcellulose 5	1.43 kg
II	Propyleneglycol	0.28 kg
III	Titanium dioxide	0.90 kg
IV	Talcum	0.90 kg
25 V	Purified water	26.70 kg

Dissolution properties of coated tablets

After 20 minutes 98.62% w/w was released (dissolution method I described herein)

- 30 Humidity (LOD): 2.4-2.6%

Conclusion

- The results obtained demonstrate that almost a 100% release and dissolution of
35 lornoxicam from lornoxicam tablets is obtainable even in a production scale.

EXAMPLE 6**Investigation on the influence of the particle size of a particulate composition on the dissolution behaviour**

5

Labtrial of tablets (particle size of the particulate composition used to prepare tablets; above or below 212 micron).

1 particulate composition batch (batch No. 08079731) was separated into two fractions,
10 i.e. fines (mean particle size (PS) < 212 micron) and coarse material (mean particle size > 212 micron). Tablets based on these two fractions (batch No. 07109731 A = < 212 μ m and batch No. 07109731 B = > 212 μ m) were manufactured.

Dissolution behaviour

15

20 min dissolution of tablets based on particulate composition with a PS < 212 μ m:

93.1%

20 min dissolution of tablets based on particulate composition with a PS > 212 μ m :

85.4%.

20

Conclusion

The particle size of the particulate composition employed in the tableting process seems to have a significant influence on the release rate. Furthermore, a smaller mean particle
25 size seems to have a better behaviour with respect to fast dissolution than a larger mean particle size.

EXAMPLE 7**30 Upscaling – production scale**

In this trail 5 batches were prepared after the same method as described in Example 5 apart from i) the type of nozzle used for atomization of the reaction medium, ii) the amount of reaction medium and iii) the reaction time. In Example 7 a shower type to the

distribution of the medium was used which do not give a real atomization. The process parameters of these trials are shown in Table 3:

Table 3

5

Trial No.	Amount of medium G/10,000 tab.	Reaction time*	+/- chopper	Release 20 min
1 (972510)	1440	16 min	-	100.4 %
2 (972520)	1440	8 min	-	99.1 %
3 (972530)	1340	16 min	-	100.2 %
4 (972540)	1340	8 min	-	-
5 (972550)	1440	6 min	+	-

*: Including time for distribution of water; approx. 2 min

The technical properties were identical to the results given in Example 5.

10 The cores were coated as described in Example 5.

20 min dissolution of coated tablets

Coated tablets of trial 1 (972560 (batch no. of the cores: 972510)): 100.4 %

15 Coated tablets of trial 2 (972570 (batch No. of the cores: 972520)): 100.4 %

Coated tablets of trial 3 (972580 (batch no. of the cores: 972530)): 99.0 %

Coated tablets of trial 4 (972600 (batch No. of the cores: 972540)): 96.1 %

Coated tablets of trial 5 (972590 (batch No. of the cores: 972550)): 94.1 %

20 The above-given results demonstrate that the amount of coating liquid and the reaction time are critical (support the results from the lab trials described in Example 1). However, the method of distribution of the reaction medium to the powder does not appear to be critical in production scale.

Conclusion

A reaction time including time for distribution of water corresponding to about 8 min seems to require at least about 1440 g of reaction medium/10,000 tablets. A reaction time including the time for distribution of water corresponding to about 6 min or below will most likely not result in a batch having a release close to 100% released after 20 min.

EXAMPLE 8

10 Investigation on the influence of sodium hydrogencarbonate and calcium hydrogen phosphate on the properties of the final composition

Labtrials investigating the influence of the particle size of critical excipients on the dissolution and/or technical properties were based on a 2^4 factorial design with 2 replication of the centrepont.

The purpose of the trials was to find the effect on the technical properties of the factors and the levels listed below.

20 19 trials have been performed. The manufacturing process used was identical to trial 1 in Example 1, however the spray pressure was fixed at 2.2 bar, the reaction time (excluding the time for distribution of water) at 16 min and the chopper was not used.

Factors	1 μm	2 μm	3 μm	4 μm
NaHCO_3	40	86	122	200
CaHPO_4	11	25*,30	60	128

25 *: The batch No. of this ingredient is identical to the batch No. used in Example 1.

20 min dissolution (for batches with a satisfactory or almost satisfactory friability), particle size of CaHPO_4 and NaHCO_3 and technical properties are shown in Table 4.

Table 4

Trial No.	NaHCO ₃ μm	CaHPO ₄ μm	Tablet Hardness	Disintegration	Friability %	Uniformity of mass (S _{rel})	Release 20 min (%)
1(180398 32)	122*	25*	92.7	6'25"	0.26/0.31	1.50	95.5
2(190398 32)	86	11	44.1	5'10"	10.4/0.31	1.50	90.5
3(230398 32)	122	60	6.9	1'37"	100	3.29	-
4(240398 32)	122	30	73.4	4'41"	0.32/0.36	2.75	90.4
5(250398 32)	200	128	48.2	4'10"	6.64/3.42	1.53	-
6(250398 34)	200	11	42.1	4'22"	6.67/9.07	3.14	-
7(250398 37)	86	30	92.5	5'42"	0.20/0.19	2.31	89.7
8(270398 32)	40	11	48.3	4'57"	58.91/29.3 1	2.57	-
9(300398 32)	200	30	90.1	4'13"	0.39/0.40	2.59	91.0
10(31039 833)	122	30	89.4	4'57"	0.32/0.38	2.92	89.6
11(02049 832)	122	11	35	3'34"	100	2.80	-
12(03049 832)	40	30	77.3	4'54"	0.39/0.37	2.60	90.9
13(06049 832)	40	128	24.8	3'06"	100	2.92	-
14(07049 832)	200	60	17.7	1'28"	100	4.04	-
15(08049 832)	122	128	20.1	2'34"	100	3.27	-
16(14049 832)	122	30	78.2	4'10"	0.29/0.32	2.16	89.8
17(14049 834)	40	60	6.3	1'28"	100	0.69	-
18(15049 832)	86	60	3.5	1'22"	100	2.11	-
19(17049 832)	86	128	28.3	2'28"	100	1.93	-

*: The batch No. of this ingredient is identical to the batch No. used in Example 1.

Anova variance analysis with respect to crushing strength and disintegration is given in the following:

Analysis of Variance – crushing strength – Type III Sums of Squares

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Main Effects					
A:CaHPO ₄	16613.9	4	4153.48	83.43	0.0000
B:NaHCO ₃	448.545	3	149.515	3.00	0.0767
Residual	547.601	11	49.7819		
TOTAL (corrected)	18128.2	18			

5 All F-ratios are based on residual mean square error.

The results given above are shown in Figs. 1 and 2 and show that the particle size of the calcium hydrogen phosphate employed has a significant influence on the crushing strength of the tablets. The particle size of the sodium hydrogencarbonate employed
10 seems to have little or no influence on the crushing strength of the tablets.

Analysis of Variance - disintegration – Type III Sums of Squares

Source	Sum of Squares	Df	Mean Square	F-Ratio	P-Value
Main Effects					
A:CaHPO ₄	138086.0	4	34521.5	25.97	0.0000
B:NaHCO ₃	3303.57	3	1101.19	0.83	0.5055
Residual	14623.8	11	1329.43		
TOTAL (corrected)	155165.0	18			

All F-ratios are based on residual mean square error.

15 The results given above are shown in Fig. 3 and show that the particle size of the calcium hydrogen phosphate employed has a significant influence on the disintegration time of the tablets whereas the particle size of the sodium hydrogencarbonate employed seems to have a much less pronounced influence on the disintegration time of the tablets.

Conclusion

The particle size of CaHPO_4 appears to have a significant effect on the technical properties (friability and disintegration time). CaHPO_4 having a mean particle size of approx. 11 μm , 60 μm and 128 μm does not give hard tablets but tablets with a friability % for most of them close to 100. However, the particle size of NaHCO_3 does not appear have a significant effect on the technical properties.

EXAMPLE 9

Water-based reaction

3 labtrials involving a reaction medium consisting solely of water were performed. The composition and manufacturing process were identical to the trials relating to the particle size in accordance with Example 8. The results of these trials are shown in Table 5.

Table 5

Trial No.	Amount of medium (g)	Amount through a 0.18 mm sieve (%)	Tablet Hardness N	Uniformity of mass (S_{rel})	Disintegration	Release 20 min.
1(20049832)	1440	92	98.6	2.70	5'01"	95.8
2(22049832)	1940	60.2	98.8	2.30	8'08"	65.8
3(23049832)	1440	91.2	96.9	2.97	5'08"	91.3

20 Conclusion

Trials 1 and 3 employing an amount of medium of 1440 g/10,000 tablets gave a release of about 91-95% w/w (dissolution method I as described herein). A higher amount of the medium (trial 2) gave a low release of 65.8% w/w and a longer disintegration time. The mean particle size of the particulate composition of trial 2 is larger than that of trial 1 and 3.

EXAMPLE 10**Upscaling – production scale**

- 5 2 trials (batch Nos. of the cores: 020590 and 020600) were prepared in production scale. The composition and manufacturing process of the cores were identical to trial 2 in Table 3 (Example 7) (scale-up 2).

The aim of this series of batches was to improve the coating process in order to minimise
10 the water content in the tablets after the coating (too high a water content may lead to degradation of lornoxicam).

A change in the coating process was carried out by increasing the product temperature during the coating with about 10°C, by lowering the liquid flow rate to about 80 g/min and
15 by introducing a 1h drying after the coating has been applied.

Technical properties of the cores

Batch No.:	020590	020600
20 Humidity (LOD):	1.33%	1.39%
Disintegration:	2 – 4 min	2 – 3 min
Tablet hardness:	90 – 120 N	90 – 120 N

20 min dissolution of the cores

25

020590: 97.3%

020600: 97.9%

20 min dissolution of coated tablets

30

021170 (batch No. of the cores: 020590): 97.6%

020640 (batch No. of the cores: 020600): 96.8%

Humidity (LOD): 1.3-1.5%

35

Conclusion

The water content of the tablets has been reduced from about 2.0 or more to values below 1.5%.

5

The small increase in the disintegration time was due to an increase in the tablet hardness of approx. 20 N.

EXAMPLE 11

10

Production scale trial with water based reaction

One batch (No. 020560) based on a reaction medium consisting solely of water was prepared in production scale. The composition and manufacturing process of the cores
15 were identical to the trials in Example 10 apart from the reaction medium, which in this example was purified water. The reaction time (including time for distribution of the water; approx. 2 min) was 16 min.

Tablets were compressed as described in Example 10.

20

Technical properties of cores

Humidity (LOD):	1.4%
Disintegration time (min):	1'30"
25 Tablet hardness:	50-70 N

20 min dissolution of the cores

The coating process was carried out with identical process parameters as described in
30 Example 10.

20 min dissolution of coated tablets

020610 (batch No. of the cores: 020560): 91% w/w
35 Humidity (LOD): 1.3%

Conclusion

A water-based reaction (in this case without any other solvent than water) in production
5 scale gave a low tablet hardness. The hardness of the tablets gave some problems during
the coating process. The release after 20 min seems to be lower compared to the results
obtained in Example 10.

EXAMPLE 12

10

**Investigation on the influence of the conjugate reaction conditions on the chemical
degradation of lornoxicam.**

The purpose of the present example was to investigate whether the reaction between an
15 active drug substance (lornoxicam) and an alkaline substance (sodium
hydrogencarbonate) suitable can be performed before any addition of other ingredients
and pharmaceutically acceptable excipients without influencing the favourable stability
characteristics with respect to chemical degradation of lornoxicam.

20 One batch (a) of tablets having the composition listed in Example 1 was manufactured as
described in Example 1 using a spray pressure of 1.3 bar, a reaction time of 9 min, an
impeller and chopper speed I and with an amount of reaction medium of 1440 g. The
cores were film coated using the film described in the following:

25	Pharmacoat 603 (HPMC)	108 g
	Macrogol 6000	9 g
	Titanium dioxide	41 g
	Talc	8 g
	Purified water	374 g
30	Ethanol	655 g

The thus coated tablets were packed in double aluminium blister packages.

A second batch (b) of tablets having the composition listed below was manufactured in
35 the following manner:

- 8 g of sodium hydrogencarbonate was dissolved in 120 g of water and mixed with a suspension of 32 g lornoxicam in 600 g of ethanol. While forming gaseous carbon dioxide, lornoxicam dissolved. 100 g of Pharmacoat 606W was added and dissolved. 212 g of sodium hydrogen carbonate was admixed and dissolved. The solution obtained was mixed with Avicel in a lab size mixer. The wet mixture was dried and then magnesium stearate and polyplasdone XL were admixed in the lab scale mixer.

	Lornoxicam	32 g
10	Sodium hydrogencarbonate	220 g
	Avicel PH 101	998 g
	Pharmacoat 606W	100 g
	Aerosil 200	12 g
	Magnesium stearate	4 g
15	Polyplasdone XL	34 g

The tablets were coated with the film coating shown in the table above. The amount of dry matter applied was adjusted to the number of tablets produced.

- 20 The coated tablets were packed in sealed glass containers.

- The two batches (a and b) - which both were packed in water tight packages – were exposed to room temperature for 6 month with an intermediate measurement after 3 months. In the following are given the results (degradation product HN 33144 is a degradation product of lornoxicam):

Batch	Degradation product HN 33144		Total amount of degradation product	
	% w/w of total weight		% w/w of total weight	
	3 months	6 months	3 months	6 months
a	0.1	0.2	0.2	0.2
b	0.8	0.7	2.6	2.9

Conclusion

The formation of a conjugate (e.g. a sodium salt of lornoxicam) before admixing the other
 5 the chemical stability of lornoxicam.

EXAMPLE 13

**Production scale investigation on the influence of the particle size of calcium
 10 hydrogen phosphate on the tablet hardness**

Production scale trials were carried out based on the findings in Example 8. The
 experiments were carried out without the addition of any therapeutically active substance.

- 15 4 trials were performed and the batches used in the trials were manufactured as
 described in Example 10 (batch size: 80 kg) with the only changes that calcium hydrogen
 phosphate was employed in qualities having a mean particle size as described below and
 that the therapeutically active substance, lornoxicam, was omitted from the compositions.
- 20 The mean particle sizes of the various qualities of the calcium hydrogen phosphate
 employed were as follows and the particle size was determined by laser light scattering:

Table 6

Trial No. (Batch No.)	Mean particle size measured (n = 2), µm	Comments	Obtained tablet hardness N (n ≥ 18)
1 (10023460)	30		101 – 126
2 (10023463)	56		41 – 62
3 (10023461)	17		96 – 115
4 (10023462)	33	Mixture 1:1 w/w of CaHPO ₄ used in trial 2 (batch No. 10023463) and in trial 3 (batch No. 10023461)	92 – 108

Conclusion

The hardness of the tablets obtained from trial No. 1 (batch No. 10023460) and trial No. 2 (batch No. 10023463) are in accordance with the findings in Example 8, namely that an increase in mean particle size leads to tablets having a decrease in the tablet hardness.

From Table 6 it is also seen that it is possible to obtain an acceptable tablet hardness even if the mean particle size is as low as 17 μm (trial 3). Furthermore, an acceptable tablets hardness can be obtained by use of a mixture of different qualities of calcium hydrogen phosphate having different mean particle size as long as the resulting mean particle size has a suitable size (neither too small nor too large), cf. trial 4. The latter is obtainable even though the particle size distribution changes.

EXAMPLE 14

15

Production scale continuation of Example 13 including incorporation of lornoxicam in the compositions

The results of Example 13 showed that both the approx. 30 μm CaHPO_4 quality and the mixture of different CaHPO_4 qualities having a resulting mean particle size of approx. 30 μm will lead to tablets with acceptable hardness. However, the tablets prepared in Example 13 were without any therapeutically active substance. Therefore, it was tested whether the same conclusion is valid for tablets containing a therapeutically active substance such as, e.g., lornoxicam.

25

The following batches were produced in the same manner as described in Example 10:

1. Batch No. 10025279 containing the same type of CaHPO_4 as in batch No. 10023460 of Example 13.
- 30 2. Batch No. 10025280 containing the same type of CaHPO_4 as in batch No. 10023460 of Example 13.
3. Batch No. 10025281 containing the same type of CaHPO_4 as in batch No. 10023462 of Example 13.
4. Batch No. 10025282 containing the same type of CaHPO_4 as in batch No. 10023462 of Example 13.

35

The following results were obtained:

Table 7

5

Trial No. (Batch No.)	Tablet hardness; Uncoated tablets	20 min. dissolution data coated tablets		
		Mean (%)	s	n
1 (10025279)	81 – 113	87.2	1.7	6
2 (10025280)	86 – 128	89.9	0.8	6
3 (10025281)	68 – 97	85.8	1.1	6
		85.4	1.4	6
4 (10025282)	87 – 110	87.5	0.5	6

s = standard deviation

n = number of tests

10 Conclusion

The hardness of the tablets from the above listed batches is satisfactory for all batches. This means that mixing of CaHPO_4 batches with different particle sizes is possible as long as the mean particle size is close to the acceptable level of approx. 30 μm . Furthermore, incorporation of lornoxicam in the compositions does not seem to have any practical influence on the tablet hardness.

EXAMPLE 15

20 Labscale trials - Effect of reducing particle size of the powder mixture after treatment with an aqueous medium

In labscale tablet cores were manufactured as described in Example 8 with the exception that the batch size was 4.48 kg (in Example 8 the batch size was 3.2 kg). The composition

of the individual tablets was identical to the composition given in Example 1. The batches were prepared using the following ingredients and amounts:

I	Lornoxicam	112.0 g
5 II	Sodium bicarbonate	560.0 g
III	Avicel PH 101	1344.0 g
IV	Calcium hydrogen phosphate anhydrous	1546.0 g
V	L-HPC	672.0 g
VI	Hydroxy propyl cellulose	224.0 g
10 VII	Purified water	1512.0 g
VIII	Ethanol 99,9 %	504.0 g
IX	Calcium stearate	5.0 g*

* amount adjusted for a total of 1 kilogram of I-VI, i.e. the content of calcium stearate is

15 5.0 g/kg.

The following results were obtained:

Table 8

Trial No. (Batch No.)	PS reduction method #	PS obtained *	Dissolution 20 min. dissolution data			Comments
			Mean	s	n	
1 (16039832)	Dry sieving; 0.7 mm	54	82.3	0.2	6	
2 (17039832)	Dry sieving; 0.6 mm	71	87.8	0.2	6	Same granulate as in trial 1 (batch No. 16039832)
3 (03039932)	Wet sieving; 0.6 mm Dry sieving; 0.7 mm	66	83.6	0.7	3	
4 (03039931)	Semiwet sieving; 0.6 mm Dry sieving; 0.7	62	83.7	0.6	3	
5 (12039932)	Comill; semidry; 0.27 mm Dry sieving; 0.7 mm	97	91.2	0.7	3	Rather time consuming
6 (28059931)	Use of chopper at high speed during all of the wet massing phase	70	89.9	1.1	6	

#: Particle Size (PS) reduction method applied during or after the granulation or drying of

20 the particulate material (dry sieving means that the reduction method is applied after

drying of the wet particulate material; wet sieving means that the reduction method is applied while the particulate material is wet and before any drying; semiwet drying means that the particulate material has almost been dried before the reduction method is applied).

5 *: % through sieve 180 μm

Conclusion

All particle reduction methods seem to be suitable. The comill method, however, seems to
10 be most efficient but it is also the most time consuming.

In accordance with Example 1 the attempt in trial No. 6 (batch No. 28059931) to avoid the formation of agglomerates by vigorous use of the chopper did only moderately improve the process as agglomerates are still present and the dissolution is still fairly low.

15

EXAMPLE 16

Labscale trials - Effect of introducing non-continuous wet-massing

20 In lab scale tablet cores were manufactured as described in Example 15 with the exception that the wet massing phase has been varied. The following batches were manufactured:

Table 9

Trial No. (batch No.)	Wet massing time*	Wet massing interruption*	20 min. dissolution #			% w/w through sieve 180 µm
			mean	s	n	
1 (12939933)	1+1+1+1	3+3+3+3	97.1	0.6	3	72
			95.3	1.3	3	
			96.5	1.3	3	
			98.0	3.7 □	3	
			96.5	3.4 □	3	
			96.5	0.8 □	3	
			96.2	0.9 □	3	
			97.2	1.4	3	
			99.1	1.4	3	
2 (16039935)	1+1+1+1	3+3+3+3	95.3	0.4	3	71
			96.4	1.4	3	
3 (16039936)	1+1+1+1	3+3+3+3	93.0	3.5	3	70
			94.5	0.8	3	
4 (23039935)	1+1	6	81.0	1.1	3	66
			86.9	1.7	6	
			85.4	2.1	6	
5 (23039936)	1+1	30	93.4	0.4	3	67
			96.7	0.8	3	
			96.7	0.6 □	3	
			94.8	2.4 □	3	
			96.5	2.1 □	3	
			95.4	1.4 □	3	
6 (26039932)	2+2+2+2	2+2+2+2	92.7	1.4	6	80
			93.5	0.2	3	
7 (26039931)	2+2+2+2 \$	2+2+2+2	89.3	1.6	6	75
			91.6	0.7	3	
8 (12049940)	1+1+1	15+15	97.6	1.8	6	69
			97.2	1.5	6	
			94.9	1.2	3	

*: the "wet massing time" and "wet massing interruption" are to be understood in the following way. Wet massing time: 1+1+1+1 and wet massing interruption 3+3+3+3 means that the granulate has been produced by the following method: 1 min wet massing

followed by 3 min interruption followed by 1 min wet massing followed by 3 min interruption and so on.

#. When more than one mean value is shown, the analysis have been repeated on tablets from the same trial No.

5 α : The data have not been corrected for variation in tablet mass

§: Rpm of impeller only half the value of the other experiments. Actual value used in trial 26039931: approx. 140 rpm.

Conclusion

10

As can be seen from the above listed data then the introduction of periods of no agitation during the wet massing phase gives dissolution data that clearly are above what could be achieved by milling the dry granulate as described in Example 15.

15 However the use of periods of no agitation must be adjusted neither to have too much nor too little agitation, i.e. energy input. As an example, in trial No. 4 (batch No. 23039935) it is clear that a too short overall wet massing has been employed (the dissolution results are fairly low), whereas in trial No. 7 (batch No. 26039931) too much agitation might have been used. Therefore the dissolution data for trials Nos. 4 and 7 are not as high as those
20 obtained from trial No. 1 (batch No. 12039933).

EXAMPLE 17

Labscale trials to test the set-up in Example 16 but employing a smaller batch size

25

Lab scale batches were manufactured as in Example 16 with the exception that the batch size has been lowered to 3.2 kg in order to test the influence of the batch size. This batch size of 3.2 kg gives the exact same composition as in Example 8. In fact batch Nos.

18039832, 24039832, 31039833 and 14049832 are from Example 8 and are quoted here

30 again to facilitate a comparison of the data.

The following results were obtained:

Table 10

Trial No. (batch No.)	Wet massing time*	Wet massing interruption*	20 min. dissolution #			% w/w through sieve 180 μ m after drying
			mean	s	n	
	min.	min.				
1 (18039832)	16	0	95.5	0.5	6	
2 (24039832)	16	0	90.4	0.6	6	
3 (31039833)	16	0	89.6	0.8	6	
4 (14049832)	16	0	89.8	1.1	6	
5 (29049932)	1+1+1	15+15	95.4	2.2	6	68
			94.3	1.8	3	
			93.6	0.2	3	
6 (28049931)	1+1+1+1	3+3+3+3	98.4	1.3	6	63
			98	1.6	3	
			9.,9	0.7	3	

*: the "wet massing time" and "wet massing interruption" are to be understood in the following way. Wet massing time: 1+1+1+1 and wet massing interruption 3+3+3+3 means that the granulate has been produced by the following method: 1 min wet massing followed by 3 min interruption followed by 1 min wet massing followed by 3 min interruption and so on.

#: When more than one mean value is shown analysis have been repeated on tablets from the same trial No.

Conclusion

The conclusion from Example 16 is also valid for the trial of Example 17 even though the batch size in Example 17 is lower. There is a marked benefit with respect to the obtained dissolution results in using the interval wet massing set up described above.

Furthermore it is interesting to note that of all of the batches from Examples 16 and 17 with different interruptions of the wet massing phase no batch has a very fine particle size. This indicates that the particle size of the particulate material is not the only parameter to influence the dissolution rate.

5

EXAMPLE 18**Lab scale trials with Ibuprofen as the therapeutically active substance**

- 10 In lab scale, 3 types of tablet cores were manufactured. The *first type* (batch No. 10059932) was manufactured as described in Example 8 with the exception that lornoxicam has been substituted with ibuprofen. Therefore, the composition was as follows:

15	I	Ibuprofen	80.0 g
	II	Sodium bicarbonate	400.0 g
	III	Avicel PH 101	960.0 g
	IV	Calcium hydrogen phosphate anhydrous	1104.0 g
	V	L-HPC	480.0 g
20	VI	Hydroxy propyl cellulose	160.0 g
	VII	Purified water	1080.0 g
	VIII	Ethanol 99,9 %	360.0 g
	IX	Calcium stearate	5.0 g/kg*

- 25 * amount adjusted for a total of 1 kilo of I-VI.

The same way of manufacturing but excluding the wet massing phase, that is manufacturing the tablets by direct compression, was used for the *second type* (batch No. 07069934) of tablet cores.

30

The *third type* (batch No. 07069933) of tablets was manufactured in the same manner as the second type, that is by direct compression, with the exception that the sodium hydrogencarbonate was omitted.

The following results were for each dissolution test based on the measurement on 15 tablets with a declared amount of Ibuprofen of 120 mg. The dissolution method used is the following:

5

Test Method

Apparatus: Ph. Eur. Dissolution test for solid dosage forms and USP XXIII <711> apparatus 2, equipped with Sotax AT7. The measurements were performed using an
10 Perkin-Elmer spectrophotometer Lambda 15.

Glass fibre filter: Whatmann GF/F

Dissolution medium: 900 ml dissolution medium. (see below)

15

Number of revolutions: 50 rpm.

Temperature of dissolution medium: $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$.

20 Measuring times: At 10, 20, 30 and 60 min. (and 180 min.)

Detection UV: 221 nm

Preparation of reagents:

25

Dissolution medium: Weigh out 50.0 g of sodium chloride and measure out 141.6 ml of concentrated hydrochloric acid. Dissolve the chemicals in distilled water and dilute to 25 l with distilled water.

30 Standards:

Stock solutions: 2 stock solutions (S_1 and S_2) with a concentration of 1000 $\mu\text{g/ml}$ Ibuprofen was prepared. Ibuprofen was dissolved in dissolution medium.

Standard: Each of the stock solutions was diluted to two standards with dissolution medium: E.g. 2.00 ml was diluted to 50.00 ml and 3.00 ml was diluted to 50.00 ml, or 2.00 ml was diluted to 50.00 ml and 4.00 ml was diluted to 50.00 ml with dissolution medium.

5 Test procedure

900 ml of dissolution medium is filled to each of the vessels (typically three or six vessels for the product). The medium is heated to $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. The product to be tested (e.g. therapeutically and/or prophylactically active substance, a particulate composition, a granulate, granules or a composition in the form of a tablet, capsules or a sachet) is placed in the vessel.

A samples volume of e.g. 10 ml is extracted and filtered at the defined times.

Samples and standards were diluted with ethanol to a suitable concentration (e.g. a 25 times dilution) before measuring.

15

Calculation for the dissolution method.

Percentage dissolved was calculated with reference to a standard of Ibuprofen.

20 Calculate the quantity (y_{10} , y_{20} , y_{30} and y_{60}) of Ibuprofen dissolved in per cent of the stated content in each of the tablets using the following expressions.

10 min.

$$y_1 = \frac{abs_{sample} \cdot stA}{abs_{std}} \cdot \frac{n \cdot 900 \cdot 100}{100 \cdot x}$$

25

20 min.

$$Z_{20} = \frac{abs_{sample} \cdot stA}{abs_{std}} \cdot \frac{n \cdot (900 - v) \cdot 100}{100 \cdot x}$$

$$y_{20} = Z_{20} + y_{10} \cdot \frac{v}{900}$$

30 min.

$$z_{30} = \frac{abs_{sample} \cdot stA}{abs_{std}} \cdot \frac{n \cdot (900 - 2v) \cdot 100}{100 \cdot x}$$

$$y_{30} = z_{30} + y_{10} \cdot \frac{v}{900} + y_{20} \cdot \frac{v}{900 - v}$$

5

60 min.

$$z_{60} = \frac{abs_{sample} \cdot stA}{abs_{std}} \cdot \frac{n \cdot (900 - 3v) \cdot 100}{100 \cdot x}$$

10

$$y_{60} = z_{60} + y_{10} \cdot \frac{v}{900} + y_{20} \cdot \frac{v}{900 - v} + y_{30} \cdot \frac{v}{900 - 2v}$$

Where

stA	=	Concentration of the standard in mg/ml.
Abs _{sample}	=	Absorption of the sample
15 Abs _{std}	=	Absorption of the standard
n	=	Potency of the standard in percent
v	=	sample amount in ml
x	=	stated content

The results obtained are the following:

Time	Batch No. 10059932		Batch No. 10059932		Batch No. 07069934		Batch No. 07069933	
	n = 2		n = 3		n = 2		n = 2	
	x	s	x	s	x	s	x	S
10 min	63.0	5.8	64.5	4.4	39.6	1.8	22.8	0.6
20 min	65.1	6.7	62.6	1.2	43.6	0.6	26.7	1.3
30 min	61.3	0.4	62.4	1.4	43.4	1.8	28.7	1.0
60 min	56.2	2.7	60.2	0.8	40.2	0.6	30.4	0.1
180			43.2	6.1				

5 Conclusion

From the data shown above it is evident that the first formulation type, that is the approach of Example 1, markedly improves the dissolution rate compared to a direct compression, irrespective of whether NaHCO_3 is present. However, the addition of NaHCO_3 in a direct compression has some effect on the dissolution rate.

EXAMPLE 19

Lab scale trials with furosemid as the therapeutically active substance

15

In lab scale, 3 types of tablet cores were manufactured. The *first type* (batch No. 06059932) was manufactured as described in Example 8 with the exception that lornoxicam has been substituted with furosemid. Therefore, the composition was as follows:

20

I	Furosemid	80.0 g
II	Sodium bicarbonate	400.0 g
III	Avicel PH 101	960.0 g
IV	Calcium hydrogen phosphate anhydrous	1104.0 g
25 V	L-HPC	480.0 g
VI	Hydroxy propyl cellulose	160.0 g

VII	Purified water	1080.0 g
VIII	Ethanol 99,9 %	360.0 g
IX	Calcium stearate	5.0 g/kg*

5 * amount adjusted for a total of 1 kilo of I-VI

The same way of manufacturing but excluding the wet massing phase, that is manufacturing the tablets by direct compression, was used for the *second type* (batch No. 04069934) of tablet cores.

10

The *third type* (batch No. 04069932) of tablets was manufactured as the second type, that is by direct compression, with the exception that sodium hydrogencarbonate was omitted.

The results given below are results for each dissolution test performed and based on a
 15 measurement on 1 tablet with a declared amount of furosemid of 8 mg. The dissolution method used is dissolution method I, only are the revolutions of the paddle changed to 50 rpm and the wavelength used is 274 nm. The substance used for standard is furosemide, the concentrations being identical to that of lornoxicam.

20

The following results were obtained:

Time	Batch No. 06059932		Batch No. 04069934		Batch No. 04069932	
	n = 2		n = 2		n = 2	
	x	s	x	s	x	s
10 min	102.4	1.4	90.2	2.6	73.8	0.2
20 min	104.7	1.8	92.3	0.3	86.0	1.4
30 min	104.5	1.0	93.9	0.9	93.1	0.7
60 min	105.1	1.2	96.7	0.1	102.2	0.7
80 min	104.3	1.2	97.3	0.3	105.1	0.6
100 min	104.3	1.3	97.5	0.1	106.8	0.4

If these data are adjusted so that the end release after 100 min equals 100 % the
 25 following data is obtained:

Time	Batch No. 06059932		Batch No. 04069934		Batch No. 04069932	
	n = 2		n = 2		n = 2	
	Org	Adj.	Org	Adj.	Org	Adj.
10 min	102.4	98.2	90.2	92.5	73.8	69.1
20 min	104.7	100.4	92.3	94.7	86	80.5
30 min	104.5	100.2	93.9	96.3	93.1	87.2
60 min	105.1	100.9	96.7	99.2	102.2	95.7
80 min	104.3	100.0	97.3	99.8	105.1	98.4
100 min	104.3	100.0	97.5	100.0	106.8	100.0

Org: = original data

Adj: = adjusted data

5 Conclusion

From the data given above it is seen that the initial release after 10 and 20 min is markedly influenced by the kind of formulation. This means that the addition of NaHCO_3 gives a markedly quicker dissolution rate. The formulation of type 1 seems to be the most effective indicating that the wet massing step is advantageous.

EXAMPLE 20

Lab scale trials - Investigation on the influence on the dissolution rate by adding sodium lauryl sulphate to lornoxicam containing compositions.

In lab scale the effect of sodium lauryl sulfate was investigated by

- granulating with a formulation in which NaHCO_3 has been substituted by sodium lauryl sulfate or
- direct compression of the formulation of Example 8 with the addition of sodium lauryl sulphate.

The actual formulation of trial a) and b) are shown below:

	Trial a; batch No. 18069932 {gram}	Trial b; batch No. 17069932 {gram}
Lornoxicam	80	80
Sodium bicarbonate	-	400
Sodium lauryl sulphate	32	32
Avicel PH 101	960	960
Calcium hydrogen phosphate anhydrous	1104	1104
L-HPC	480	480
Hydroxy propyl cellulose	160	160
Purified water	955,5	-
Ethanol 99,9 %	318,5	-
Calcium stearate	5 g/kg*	5 g/kg*

*: adjusted for 1 kg of particulate material

- 5 The composition of trial a was manufactured as described in Example 8) and the composition of trial b was manufactured by direct compression (i.e. omitting the wet massing phase).

The results obtained were the following:

10

Time [min]	Trial a, batch No. 17069932 n = 3		Trial b, batch No 18069932 n = 3	
	x	s	x	s
10	25.1	1.1	23.0	0.5
20	28.2	0.6	28.0	0.2
60	30.9	0.5	32.2	0.1
120	32.0	0.6	33.9	0.1

Conclusion

From the results given above it is seen that the addition of a surface active agent like sodium lauryl sulphate does not lead to a quick release of lornoxicam. The same result is
5 seen in the case where sodium hydrogencarbonate as well as sodium lauryl sulphate are present in the composition.

CLAIMS

1. A quick release pharmaceutical composition for oral administration comprising a therapeutically and/or prophylactically active substance which has a solubility of at the most about 0.1 % w/v in 0.1 N hydrochloric acid at room temperature,

- the composition being based on a powder comprising the therapeutically and/or prophylactically active substance and having such a particle size that - when the powder is subjected to a sieve analysis - then at least about 90% w/w such as, e.g. at least about 92% w/w, at least about 94% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 97% w/w, at least about 98% w/w or at least about 99% w/w of the particles passes through sieve 180 μ m, the powder being contacted with an aqueous medium to form a particulate composition, which has such a particle size that - when the particulate composition is subjected to a sieve analysis - then at least about 50% w/w such as, e.g., at least about 55% w/w, at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w or at least about 95% w/w of the particles passes through sieve 180 μ m, and
- the composition - when tested in accordance with the dissolution method I defined herein employing 0.07 N hydrochloric acid as dissolution medium - releases at least about 50% w/w of the active substance within the first 20 min of the test.

2. A quick release pharmaceutical composition for oral administration comprising a therapeutically and/or prophylactically active substance which has a solubility of at the most 0.1 % w/v in 0.1 N hydrochloric acid at room temperature,

- the composition being in the form of a particulate composition or being based on a particulate composition which is obtained by contacting a powder comprising the therapeutically and/or prophylactically active substance with an aqueous medium in such a manner that the mean particle size of the particles of the particulate composition is at the most about 100% larger than the mean particle size of the powder before contact with the aqueous medium, and

the composition - when tested in accordance with the dissolution method I defined herein employing 0.07 N hydrochloric acid as dissolution medium - releases at least about 50% w/w of the active substance within the first 20 min of the test.

- 5 3. A quick release pharmaceutical composition for oral administration comprising a therapeutically and/or prophylactically active substance which has a pK_a value of at the most about 5.5, such as, e.g., at the most about 5.3, at the most about 5.2, at the most about 5.0 such as, e.g., in a range of from about 3.4 to about 5.0 or in a range of from about 4.0 to about 5.0,

10

- the composition being based on a powder comprising the therapeutically and/or prophylactically active substance and having such a particle size that - when the powder is subjected to a sieve analysis - then at least about 90% w/w such as, e.g. at least about 92% w/w, at least about 94% w/w, at least about 95% w/w, at least about 96% w/w, at
15 least about 97% w/w, at least about 97% w/w, at least about 98% w/w or at least about 99% w/w of the particles passes through sieve 180 μm , the powder being contacted with an aqueous medium to form a particulate composition, which has such a particle size that - when the particulate composition is subjected to a sieve analysis - then at least about 50% w/w such as, e.g., at least about 55% w/w, at least about 60% w/w, at least about
20 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w or at least about 95% w/w of the particles passes through sieve 180 μm , and

- the composition - when tested in accordance with the dissolution method I defined herein
25 - releases at least about 50% w/w of the active substance within the first 20 min of the test.

4. A quick release pharmaceutical composition for oral administration comprising a therapeutically and/or prophylactically active substance which has a pK_a value of at the
30 most about 5.5, such as, e.g., at the most about 5.3, at the most about 5.2, at the most about 5.0 such as, e.g., in a range of from about 3.4 to about 5.0 or in a range of from about 4.0 to about 5.0,

- the composition being in the form of a particulate composition or being based on a
35 particulate composition which is obtained by contacting a powder comprising the

therapeutically and/or prophylactically active substance with an aqueous medium in such a manner that the mean particle size of the particles of the particulate composition is at the most about 100% larger than the mean particle size of the powder before contact with the aqueous medium, and

5

the composition - when tested in accordance with the dissolution method I defined herein - releases at least about 50% w/w of the active substance within the first 20 min of the test.

- 10 5. A composition according to any one of the preceding claims, wherein the composition – when subjected to dissolution method I as defined herein employing 0.07 N hydrochloric acid as dissolution medium – releases at least 55% w/w such as, e.g., at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w, at least about 95% w/w,
15 at least about 96% w/w, at least about 97% w/w, at least about 98% w/w or at least about 99% w/w of total amount of active substance present in the composition within the first 20 min of the test.

6. A composition according to any one of the preceding claims wherein the solubility of the
20 therapeutically and/or prophylactically active substance in 0.1 N hydrochloric acid at room temperature is at the most about 0.05% w/v such as at the most about 0.01% w/v, at the most about 0.009% w/v, at the most about 0.008% w/v, at the most about 0.007% w/v, at the most about 0.006% w/v, at the most about 0.005% w/v, at the most about 0.004% w/v, at the most about 0.003% w/v, at the most about 0.002 % w/v or at the most about
25 0.001% w/v.

7. A composition according to any one of the preceding claims, wherein the therapeutically and/or prophylactically active substance – when tested by solubility method I described herein – has such a dissolution rate that it allows an amount of at the
30 most 50% w/w of the active substance to be dissolved within the first 20 min of the test.

8. A composition according to any one of the preceding claims, wherein the composition is in the form of a solid composition.

9. A composition according to any one of the preceding claims, wherein the composition is in the form of a particulate composition.
10. A composition according to any one of the preceding claims in the form of a unit dosage form.
11. A composition according to any one of the preceding claims, wherein the aqueous medium comprises water and an organic solvent.
- 10 12. A composition according to any one of the preceding claims, wherein the mean particle size of the particles of the particulate composition is at the most about 250 μm , such as, e.g. at the most about 240 μm , at the most about 230 μm , at the most about 220 μm , at the most about 210 μm , at the most about 200 μm , at the most about 190 μm , at the most about 180 μm , at the most about 175 μm , at the most about 150 μm , at the most about 125 μm , at the most about 100 μm , at the most about 90 μm , at the most about 80 μm or at least at the most about 75 μm , whenever appropriate, after contact with an aqueous medium.
- 15 13. A composition according to any one of the preceding claims further comprising at least one pharmaceutically acceptable excipient.
- 20 14. A composition according to claim 13, wherein the at least one pharmaceutically acceptable excipient is selected from the group consisting of binders, disintegrants, fillers and diluents.
- 25 15. A composition according to claim 14, wherein the composition comprises a filler having binding properties.
16. A composition according to claim 15, wherein the filler having binding properties is, e.g., lactose (such as, e.g., Tabletose®, Pharmatose®), sugar derivatives (such as, e.g., mannitol, sorbitol), calcium carbonate (CaCO_3), tricalcium phosphate ($\text{Ca}_5(\text{PO}_4)_3\text{OH}$), calcium hydrogen phosphate (CaHPO_4) (such as, e.g., Di-Cafos®, Di-Tab®, Emcompress® or Pharmacompress®), or the like and/or mixtures thereof.
- 30

17. A composition according to claim 16, wherein the filler having binding properties is calcium hydrogen phosphate.

18. A composition according to any one of claims 15-17, wherein the filler having binding
5 properties as raw material has a mean particle size of at the most about 140 μm , such as, e.g., at the most about 130 μm , at the most about 120 μm , at the most about 110 μm , at the most about 100 μm , at the most about 90 μm , at the most about 80 μm , at the most about 70 μm , at the most about 60 μm , at the most about 50 μm , at the most about 40 μm , at the most about 35 μm , at the most about 30 μm or at the most about 25 μm such
10 as, e.g., in a range of from about 10 μm to about 80 μm or in a range of from about 15 μm to about 55 μm .

19. A composition according to any one of the preceding claims further comprising an alkaline substance such as, e.g., an antacid or an antacid-like substance.

15

20. A composition according to claim 19, wherein the alkaline substance is an antacid or an antacid-like substance such as, e.g., sodium hydrogen carbonate, magnesium carbonate, magnesium hydroxide or magnesium metasilicate aluminate or mixtures thereof.

20

21. A composition according to claim 19 or 20, wherein the mean particle size of the antacid-like substance as raw material is at the most about 250 μm , such as at the most about 225 μm , at the most about 200 μm , at the most about 175 μm , at the most about 150 μm , at the most about 145 μm , at the most about 140 μm , at the most about 135 μm ,
25 at the most about 130 μm such as, e.g., in a range of from about 20 μm to about 250 μm , in a range of from about 40 μm to about 200 μm , in a range of from about 60 μm to about 175 μm , in a range from about 80 μm to about 150 μm or in a range of from about 100 μm to about 120 μm .

30 22. A composition according to any one of the preceding claims, wherein a particulate composition further has been processed to obtain a composition in the form of tablets, capsules or sachets.

23. A composition according to any one of the preceding claims in the form of tablets.

35

24. A composition according to claim 23 obtainable by compressing a powder comprising the therapeutically and/or prophylactically active substance and at least one pharmaceutically acceptable excipient into tablets.
- 5 25. A composition according to any of claims 22-24, wherein the composition has such a mechanical strength as to enable handling and coating in a conventional coating apparatus.
- 10 26. A composition according to claim 25, wherein the composition - when subjected to a crushing strength test in accordance with Ph. Eur. - has a crushing strength of at least about 50 N such as, e.g., at least about 60 N, at least about 70 N, at least about 80 N such as, e.g., in a range from about 50 N to about 150 N, in a range of from about 60 N to about 130 N, in a range from about 70 N to about 120 N or in a range of from about 75 N to about 110 N such as from about 80 to about 100 N.
- 15 27. A composition according to any one of claims 22-26 comprising a first pharmaceutically acceptable excipient which imparts a suitable robustness to the composition to enable handling and, if desired, coating in a coating apparatus.
- 20 28. A composition according to claim 27, wherein the first pharmaceutically acceptable excipient is a filler having binding properties.
- 25 29. A composition according to any one of claims 26-28, wherein the composition - when tested as a composition without the first pharmaceutically acceptable excipient in the crushing strength apparatus according to Ph. Eur. - has a crushing strength of less than about 45 N such as, e.g., less than about 30 N, less than about 25 N, less than about 20 N, less than about 15 N or less than about 10 N.
- 30 30. A composition according to claim 28, wherein the filler having binding properties is, e.g., lactose (such as, e.g., Tabletose®, Pharmatose®), sugar derivatives (such as, e.g., mannitol, sorbitol), calcium carbonate (CaCO_3), tricalcium phosphate ($\text{Ca}_5(\text{PO}_4)_3\text{OH}$), calcium hydrogen phosphate (CaHPO_4) (such as, e.g., Di-Cafos®, Di-Tab®, Emcompress® or Pharmacompress®), or the like and/or mixtures thereof.

31. A composition according to any one of the preceding claims, wherein the therapeutically and/or prophylactically active substance is a non-steroid anti-inflammatory drug substance (NSAID substance).
- 5 32. A composition according to any one of the preceding claims, wherein the therapeutically and/or prophylactically active substance is selected from the group consisting of lornoxicam, diclofenac, nimesulide, ibuprofen, piroxicam, piroxicam (betacyclodextrin), naproxen, ketoprofen, tenoxicam, aceclofenac, indometacin, nabumetone, acemetacin, morniflumate, meloxicam, flurbiprofen, tiaprofenic acid,
- 10 proglumetacin, mefenamic acid, fenbufen, etodolac, tolfenamic acid, sulindac, phenylbutazone, fenoprofen, tolmetin, acetylsalicylic acid, dexibuprofen, paracetamol, and pharmaceutically acceptable salts, complexes and/or prodrugs thereof and mixtures thereof.
- 15 33. A composition according to any one of the preceding claims, wherein the therapeutically and/or prophylactically active substance is lornoxicam or a pharmaceutically acceptable salt, complex or prodrug thereof.
34. A composition according to any one of the preceding claims, wherein the
- 20 therapeutically and/or prophylactically active substance is present in the composition in an amount which is sufficient to give an enhanced onset of the effect.
35. A composition according to any one of the preceding claims comprising a further active drug substance.
- 25 36. A composition according to claim 35, wherein the further active drug substance is an antidepressant, an opioid, a prostaglandine analogue (e.g. misoprostol), a glucocorticosteroid, a cytostaticum (e.g. methotrexate), a H₂ receptor antagonist (e.g. cimetidine, ranitidine), a proton pump inhibitor (e.g. pantoprazole, omeprazole,
- 30 lansoprazole) and/or an antacidum.
37. A composition according to claim 35, wherein the further active drug substance is paracetamol, penicillamine, sulfasalazine and/or auranofin.

38. A composition according to any one of the preceding claims in unit dosage form, wherein the unit dosage of the composition comprises from about 1 to about 32 mg of the therapeutically and/or prophylactically active substance.
- 5 39. A composition according to any one of claims 1-37 in unit dosage form, wherein the unit dosage comprises from about 1 mg to about 1.6 g such as from about 1 mg to about 1.2 g of the therapeutically and/or prophylactically active substance.
40. A composition according to any one of claims 1-37 in unit dosage form, wherein the
10 unit dosage comprises from about 50 mg to about 1.1 g of the therapeutically and/or prophylactically active substance.
41. A composition according to any one of claims 1-37 in unit dosage form, wherein a unit dosage comprises from about 100 mg to about 1.0 g of the therapeutically and/or
15 prophylactically active substance.
42. A composition according to any one of claims 1-37 in unit dosage form, wherein a unit dosage comprises from about 200 mg to about 900 mg of the therapeutically and/or
20 prophylactically active substance.
43. A composition according to any one of claims 1-37 in unit dosage form, wherein a unit dosage comprises from about 300 mg to about 800 mg of the therapeutically and/or prophylactically active substance.
- 25 44. A composition according to any one of the preceding claims, wherein the therapeutically and/or prophylactically active substance is lornoxicam and a unit dosage of the composition contains 4, 8, 12, 16, 20, 24, 28, 32 or 36 mg of lornoxicam.
45. A composition according to any one of the preceding claims, wherein the water
30 content in the composition is at the most about 5% w/w such as, e.g., at the most about 4% w/w, at the most about 3%, at the most about 2% w/w, at the most about 1.5% w/w, at the most about 1.3% w/w, at the most about 1.1% w/w or at the most about 0.9% w/w determined by the LOD (loss on drying) method described herein.

46. A composition according to any one of the preceding claims comprising sodium hydrogen carbonate.

47. A composition according to any one of the preceding claims comprising calcium
5 hydrogen phosphate.

48. A composition according to any one of the preceding claims, wherein the composition is coated with a coat which does not substantially retard the release of the therapeutically and/or prophylactically active substance from the composition.

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49. A composition according to any one of the preceding claims, wherein the composition is coated with a film coating.

50. A method for the preparation of a composition according to any one of the preceding
15 claims, the method comprising the steps of

- i) mixing the therapeutically and/or prophylactically active substance with a) an alkaline substance, b) a filler having binding properties, and, optionally, c) other pharmaceutically acceptable excipients to obtain a powder mixture,
20
- ii) contacting the thus obtained powder mixture with an aqueous medium to obtain a wet powder,
- iii) drying the thus obtained wet powder at a temperature above room temperature until
25 the water content in the powder is at the most about 5% w/w determined as described herein, to obtain a first particulate mixture,
- iv) sieving the thus obtained first particulate mixture,
- 30 v) optionally, adding any further pharmaceutically acceptable excipients to obtain a second particulate mixture,
- vi) optionally, compressing the thus obtained second particulate mixture into tablets,
and

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vii) optionally, coating the thus obtained tablets.

51. A method according to claim 50, wherein step ii) is performed in a suitable apparatus which enables an energy input which is sufficient to bringing the particles in contact with the aqueous medium without substantially deteriorate the stability of the final composition.

52. A method according to claim 50, wherein step ii) is performed in a suitable apparatus which enables an energy input which is sufficient to bringing the therapeutically and/or prophylactically active substance and the alkaline substance in contact with the aqueous medium without negatively influencing the release rate of the active substance from the final composition.

53. A method according to claim 51 or 52, wherein the energy input is provided discontinuous.

54. A method according to any one of claims 50-53, wherein step ii) is performed in intervals of wet-massing and wet-resting.

55. A method according to any one of claims 50-54, wherein the alkaline substance employed in step i) is an antacid-like substance such as, e.g., sodium hydrogen carbonate, magnesium carbonate, magnesium hydroxide or magnesium metasilicate aluminate or mixtures thereof.

56. A method according to any one of claims 50-55, wherein the filler having binding properties is, e.g., lactose (such as, e.g., Tabletose®, Pharmatose®), sugar derivatives (such as, e.g., mannitol, sorbitol), calcium carbonate (CaCO_3), tricalcium phosphate ($\text{Ca}_5(\text{PO}_4)_3\text{OH}$), calcium hydrogen phosphate (CaHPO_4) (such as, e.g., Di-Cafos®, Di-Tab®, Emcompress® or Pharmacompress®), or the like and/or mixtures thereof.

57. A method according to any one of claims 50-56, wherein the aqueous medium employed in step ii) is a solvent comprising water and an organic solvent.

58. A method according to claim 57, wherein the organic solvent is a solvent which is miscible with water such as, e.g., a branched or unbranched lower (C_1 - C_5) aliphatic alcohol like, e.g., ethanol, methanol, isopropanol, 1-propanol, 1-butanol, 2-butanol, iso-

butanol, tert. butanol and 1-pentanol, 2-pentanol, 3-pentanol, iso-pentanol and tert. pentanol and mixtures thereof.

59. A method according to claim 58, wherein the concentration of the organic solvent in
5 the solvent is from about 0% v/v to about 95% v/v such as, e.g., from about 10% v/v to about 90% v/v, from about 10% v/v to about 80% v/v, from about 15% v/v to about 70% v/v, from about 15% v/v to about 60% v/v, from about 20% v/v to about 50% v/v, from about 20% v/v to about 40% v/v, from about 25% v/v to about 35% v/v such as, e.g. about 33.3% v/v.

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60. A method according to any one of claims 50-59, wherein step ii) is performed in a conventional high shear mixer employing an energy input which is sufficient to enable a contact to take place between the therapeutically and/or prophylactically active substance and the alkaline substance employed in step i) but at the same time is sufficiently low to
15 avoid formation of a large amount of agglomerates during the mixing.

61. A method according to any one of claims 50-60, wherein the mean particle size of the particles of the first particulate mixture is at the most about 100% larger than the mean particle size of the powder mixture from step i) before subjecting the powder mixture to
20 the reaction in the aqueous medium employed in step ii).

62. A method according to claim 61, wherein the mean particle size of the particle of the first particulate mixture is at the most 90% such as, e.g., about 80%, about 75%, about 70%, about 65%, about 60%, about 55% or about 50% larger than the mean particle size
25 of the powder mixture from step i) before subjecting the powder mixture to the reaction in an aqueous medium employed in step ii).

63. A method according to any one of claims 50-62, wherein the powder obtained in step i) has such a particle size that - when the powder is subjected to a sieve analysis - then
30 at least about 90% w/w such as, e.g. at least about 92% w/w, at least about 94% w/w, at least about 95% w/w, at least about 96% w/w, at least about 97% w/w, at least about 97% w/w, at least about 98% w/w or at least about 99% w/w of the particles passes through sieve 180 μ m, and the first particulate mixture obtained in step iii) has such a particle size that - when the particulate composition is subjected to a sieve analysis - then at least
35 about 50% w/w such as, e.g., at least about 55% w/w. at least about 60% w/w, at least

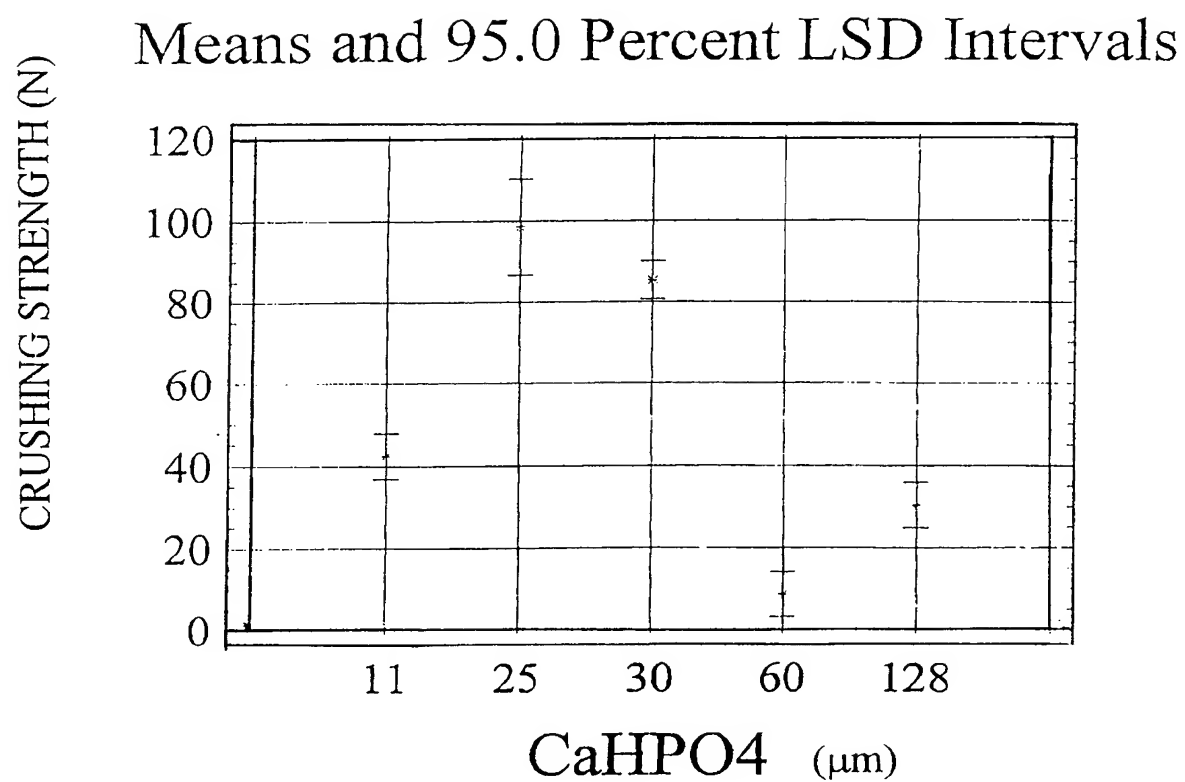
about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w or at least about 95% w/w of the particles passes through sieve 180 μm .

- 5 64. A method according to any one of claims 50-63, wherein the mean particle size of the particles of the first particulate mixture is at the most about 250 μm , such as, e.g. at the most about 240 μm , at the most about 230 μm , at the most about 220 μm , at the most about 210 μm , at the most about 200 μm , at the most about 190 μm , at the most about 180 μm , at the most about 175 μm , at the most about 150 μm , at the most about 125 μm ,
10 at the most about 100 μm , at the most about 90 μm , at the most about 80 μm or at the most about 75 μm .

65. A method for treatment and/or prophylaxis of acute pain and/or mild or moderate pain comprising administering to a patient an effective amount of a therapeutically and/or
15 prophylactically active substance in the form a quick release composition according to any one of claims 1-49.

66. A method for fast relief of acute pain comprising administering to a patient in need thereof an effective amount of a therapeutically and/or prophylactically active
20 substance in the form a quick release composition according to any one of claims 1-49.

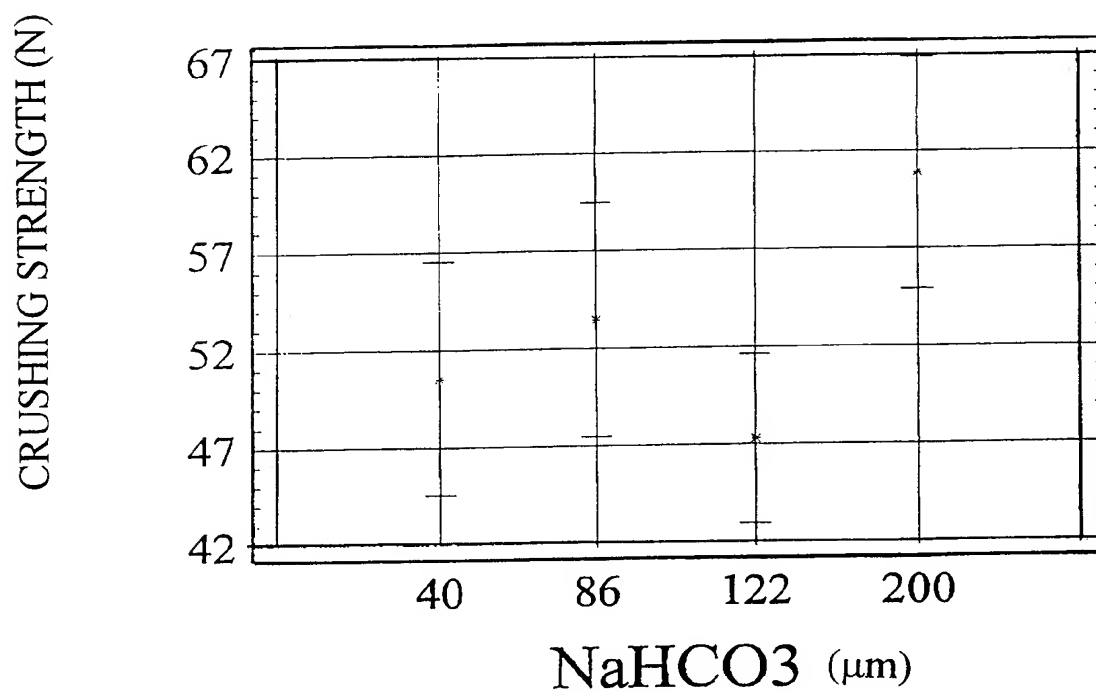
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**Fig. 1**

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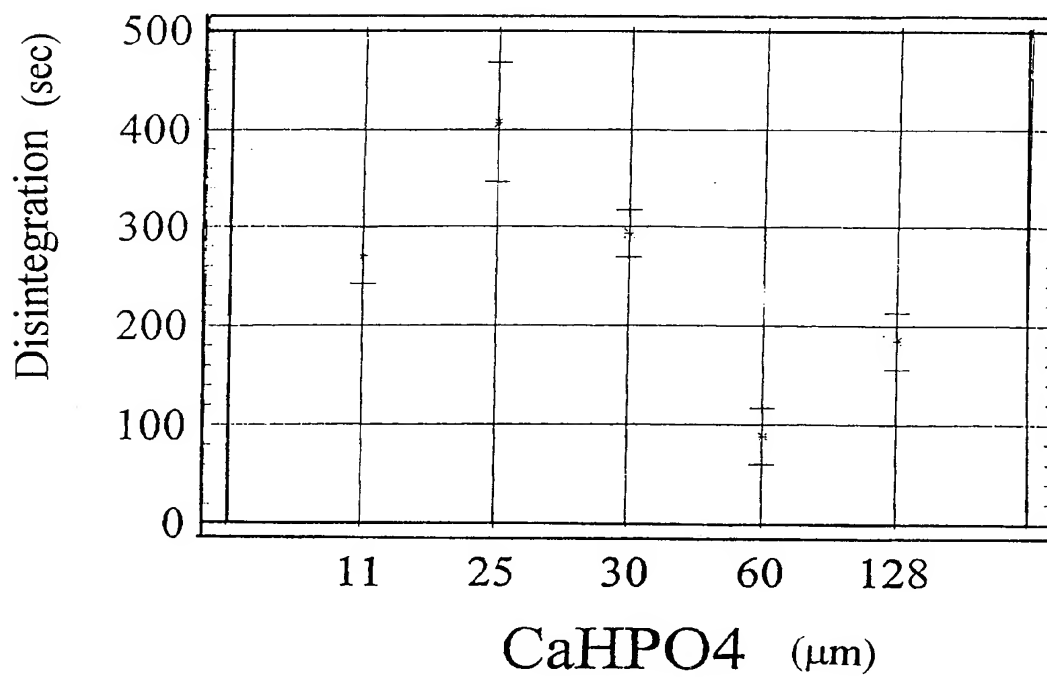
Means and 95.0 Percent LSD Intervals

**Fig. 2**

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Means and 95.0 Percent LSD Intervals

**Fig. 3**

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INTERNATIONAL SEARCH REPORT

In International Application No

PCT/DK 99/00480

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/16 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 14839 A (SOUTH AFRICAN DRUGGISTS LIMITED) 23 May 1996 (1996-05-23) the whole document ---	1-66
A	WO 95 32737 A (SOUTH AFRICAN DRUGGISTS LIMITED) 7 December 1995 (1995-12-07) the whole document --- -/-	1-66

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

3 February 2000

Date of mailing of the international search report

10/02/2000

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Ventura Amat, A

INTERNATIONAL SEARCH REPORT

Int ional Application No

PCT/DK 99/00480

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CHEMICAL ABSTRACTS, vol. 116, no. 10, 9 March 1992 (1992-03-09) Columbus, Ohio, US; abstract no. 91424, NEMOTO, MASAMI ET AL: "Solid preparations with accelerating absorption of oxicam-type anti-inflammatory agents for internal use" XP002095848 abstract & JP 03 240729 A (TAISHO PHARMACEUTICAL CO., LTD., JAPAN)</p> <p>-----</p>	1-66

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 99/00480

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 65-66 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/DK 99/00480

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